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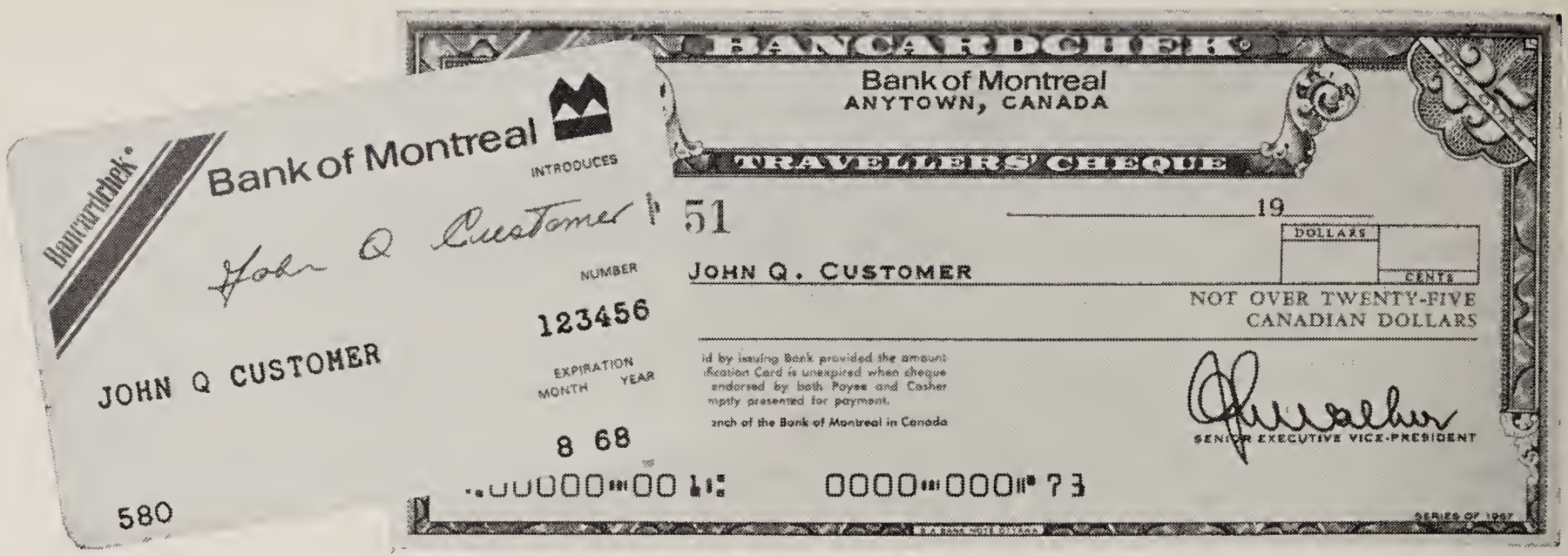
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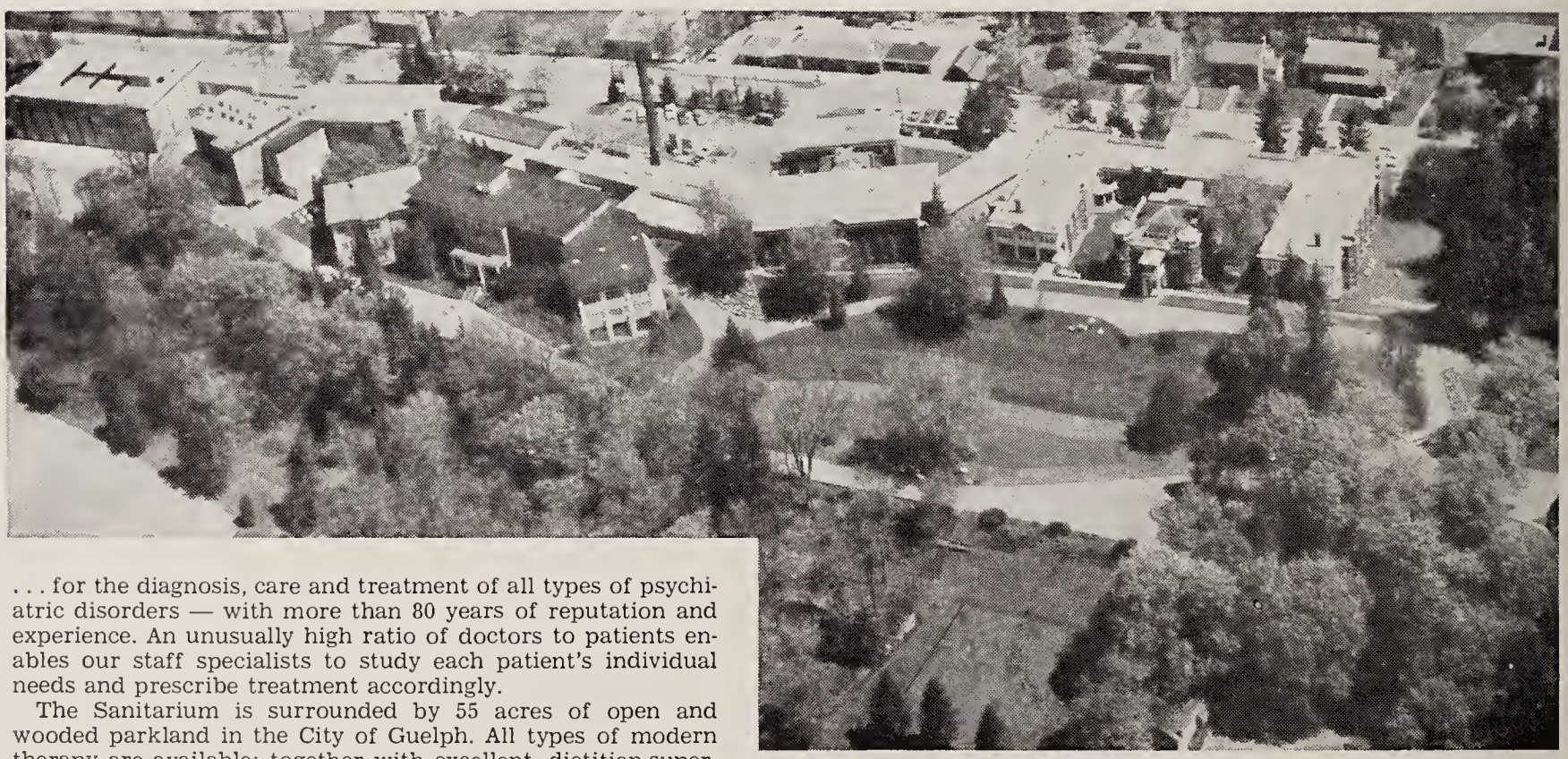
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## *Guest Editorial*

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*After internship at the Toronto General Hospital and one year of general practice in Port Credit, Dr. Wilson began his specialty training in Obstetrics and Gynaecology at the University of Toronto. Receiving his fellowship in 1960, he became a research fellow in Biochemistry and Pathological Chemistry at U. of T. As a research fellow at Clarke University, Worcester, Mass., and the Worcester Foundation for Experimental Biology, Shrewsbury, Mass., he trained in Steroid Biochemistry. Dr. Wilson, in 1962-63, was research associate with Dr. Egon Diczfalusy in the Hormone Laboratory, Dept. of Women's Diseases, Karolinska Hospital, Stockholm, Sweden.*

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# *Obstetrics And Gynaecology: A Challenge*

*"There is beauty in every woman . . . whenever a man takes time to seek it."*

Three of the most common reasons given by physicians for entering the specialty of Obstetrics and Gynaecology are the desire to associate professionally with young adults, to practice in many environments and apply the entire spectrum of medical skills, and to achieve an end result which is, in most instances, the one desired by both the physician and the patient.

The declining birth rate in Canada and the rest of North America has led to some speculation regarding the future of Obstetrics as a clinical specialty. At the the same time, the practice of Gynaecology, traditionally surgically oriented, is undergoing major alterations in the pattern of practice — towards medical rather than surgical management. Changes are occurring, not because Obstetrics and Gynaecology is a simple, narrow, and possibly obsolete specialty; but because of advances made in the understanding of disease, and the higher quality of care being rendered. The crisis-oriented problems are being resolved; and the discipline is turning to more complex problems of health care, and to a much wider definition of health itself. The practicing obstetrician and gynaecologist has found that he has had to broaden his outlook to assume the responsibilities which new health care delivery and educational systems impose upon him.

The modern obstetrician and gynaecologist deals with "systems" and "sex" . . . both of which are "timely" in relationship to current concepts of medical education and the interests of society. Indeed, the family obstetrician and gynaecologist may be the only member of the present health care team delivering preventive care in a continuing sense. The personal relationship which develops between a woman and the physician who advises and guides her through pregnancy and the birth of her children is unique. He is familiar with all the problems . . . social, economic, and medical . . . which occur in the families of his patients. He acts as confidant and psychiatrist, assists in planning the size of the family, prevents its undesired growth, and is primarily responsible for the health and function of the woman about whom the family unit revolves. In this role of physician, surgeon, midwife and counsellor, he is carrying out alone those activities which are most frequently ascribed to the health care team of the future. A convincing argument can be made for the obstetrician and gynaecologist as the primary care physician of the fture.

The numerous unanswered questions encountered by the obstetrician and gynaecologist . . . all in one way or another related to the reproductive system and sexual function . . . lead the members of the specialty, by desire and necessity, into nearly every area of the behavioural and biological sciences. The ramifications of

fertility and family planning are almost boundless. If the obvious crisis of the increasing world population is set aside, the functioning or malfunctioning of the female reproductive system leads to unknown areas of endocrinology, biochemistry, physiology, and human behaviour. The obstetrician and gynaecologist is the physician most frequently faced by the little girl with precocious puberty, the adolescent with amenorrhea, the young woman desiring premarital and family planning advice, the woman with excessive hair growth, the infertile couple, and the frigid wife. We are beginning to understand mechanisms involved in some of these situations, but the majority remain unsolved and require intensive investigation.

The effect of pregnancy upon the mother, and the effect of maternal disease and medication upon the fetus, are in early stages of research. Once again, the man who must deal with congenital abnormalities in the newborn, and fetal wastage due to prematurity or intercurrent maternal disease, is the obstetrician and gynaecologist. Progress is being made, and researchers have recently tested and proven therapeutic measures by which Rh-isoimmunization may well be eliminated. Fetal monitoring during pregnancy and labour is becoming more commonplace through the use of maternal estrogen excretion, fetal scalp sampling, and electrocardiography; but we are only beginning to have some understanding of the dynamics of pregnancy and labour.

The question of the "rejection" mechanism in organ transplantation may well be resolved through an understanding of the mechanisms by which a pregnancy, which is genetically and immunologically different from its host, is maintained within the uterine environment. We are only starting to examine the fetus, and its interactions with the maternal systems; but we see the end results every day in the delivery room.

Human sexual behaviour, and the impact of internal and external environmental stimuli upon it, is completely ignored by most modern medical school curricula. The obstetrician and gynaecologist is the health scientist who must deal with problems of sexual incompatibility and abnormal behaviour in the female. The usual amateur attempt to give guidance with knowledge procured through personal experience, or by reading the limited amount of available data, does not answer the health needs of the community. The medical profession, with some justification, has looked askance upon studies carried out in these supposedly "sensitive" areas; but the magnitude of the problem will not allow this attitude to persist. Scientific objective studies must be begun in this admittedly difficult area.

It has been, and remains, fashionable for a woman to choose an obstetrician and gynaecologist of her own age group when she first seeks premarital or family planning advice. As the years pass, and the character of the care which her physician renders changes, more and more women wish to observe degenerative processes occurring in their doctors, rather than in themselves. Hormonal replacement therapy during the perimenopausal and post-menopausal years is becoming increasingly demanded and accepted as a justifiable therapeutic measure. The mechanisms of cardiovascular, skeletal, and other degenerative changes associated with the post-menopause, and the relationship of hormonal replacement therapy to them, remain unclear. Few well documented studies have been carried out; and while many emotional opinions are expressed by health professionals, little objective data is still available. The numbers of women receiving such therapy are increasing in geometric proportion, and the biochemical mechanisms and physiological effects must be clarified. The ever enlarging group of post-menopausal women in our society will force us to adopt some objective therapeutic attitudes, regardless of our personal feelings.

Today, the obstetrician and gynaecologist finds his activities at the very center of proposed future health care delivery systems; and his patients have asked him to assume the responsibility for the existence, health, and welfare of the generations of the future. There is little doubt that the traditional concept of the discipline is changing, from one specializing in the mechanics of midwifery and surgery, to one which deals with the understanding of the very core of human survival and behaviour.

*Richard Wilson, M.D.*

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## ***Editorial*** — *On The Sexual Revolution And Our Forthcoming Role In The Community*

Out-of-wedlock births, illegal abortions, children being raised by parents who are themselves children, or by no parents at all, broken marriages at all ages, homosexuality, venereal disease — these and other problems relating to human sexual behaviour can no longer be ignored. Whether we wish to avoid these dilemmas or not is of no consequence — we will face such issues and we will be forced to take stands.

Yet how inadequately do our medical schools prepare us as physicians to deal with the nature of human sexual behaviour. The obligation to cope constructively with these matters rests with the professionals in all fields of family service. It is not enough for us to shake our heads in moralistic judgment, and before we can properly handle our roles we must come to terms with sexuality.

Mankind, in all its history, has never been caught in the forces of such violent social change as we are today. Such movies as "The Graduate" show that it is not enough for one generation to blatantly condemn another; each one being a product of its own inconsistencies. Young people cannot rightfully be criticized for a lack of responsibility while they are being walled off in a kind of adolescent dream world where they have no chance to participate meaningfully as necessary members of a community. We can no longer propose the "double standard". It is incongruous to suggest that premarital sexual exprience for young males is necessary and inevitable and yet taking for granted that the source of such experiences will not be our own daughters or sisters. It is nonsensical to regard as non virginal the girl who for example has had a single sexual experience through rape, while praising as virginal the girl who repeatedly has every part of her body explored *PROVIDED* the male penis does not enter her vagina.

And so to be faced is the sexual revolution. From the basic need and drive that it is, just as is the desire for food or for the quenching of thirst, sex has become a tool exploited by commercial interests. Advertising orientated around sex, girlie magazines, pornographic literature and sex based movies are all on the rampage. And in so doing sex has been lost sight of as a deep form of communication in one of the greatest human relationship that we know. Understanding will come only with the recognition that sex is not something we DO but something we ARE. We have been made male and female, rather than hermaphrodites, so that we can come together in this unique fashion. Only when we realize the naturalness of this act, that it has no association with dirt, will sex fall into its proper perspective as a manifestation of the more meaningful concepts of love and above all respect.

Do such suggestions about the naturalness of sex predispose to promiscuity? — Not so. Man who is gifted with reason is fully aware that without his will he is born and against his will he dies. He is aware of his aloneness and separateness and of his basic helplessness before the forces of nature and society. The sexual act without love never bridges the gap between two human beings, or alleviates their sense of aloneness — except momentarily. Modern society puts sex on a pedestal as the be all and end all of a relationship, hence distorting its significance. By accepting the commoness of sex do we enhance the chance of more meaningful approaches to the relationship between man and woman. Premarital sex does not equilibrate with promiscuity; perchance it may ensure success in marriage in that the couples can acknowledge that their attachment is not momentary (as sex alone would have indicated), but rather stems from genuine love. Perhaps it is better to have sex before marriage and the chance of a lasting nuptial tie, rather than sex confined only to a union that soon crumbles once the novelty wears off and the reality is faced that the more meaningful and lasting bonds of successful marriage were never really there. All this does not mean to imply that premarital sex is manditory but that it can no longer be so readily condemned in such a Victorian fashion as it is today.

Physicians who are on the receiving end of the troubles and burdens of human beings are going to play active roles in helping mankind to take stock of these realities. As we begin to solve the unknown realms of the physiology of pregnancy, the hormonal factors affecting reproduction and sexual drives, and the complex nature of infertility, or the as yet to be understood sequelae of contraception we will improve our medical handling of these problems. When we compound these advances with our own more mature outlooks the future role of the obstetrician and gynecologist and the physician in dealing with mankind and his necessary and inevitable social changes will indeed be a fascinating challenge. We should all be looking forward to our future roles. H.P.D.

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The Editors wish to express their thanks to Dr. William M. Paul and Dr. William H. Allemange of the Department of Obstetrics and Gynecology, University of Toronto, and the Toronto General Hospital for their advice in the preparation of this Journal. H.P.D. and J.K.F.

# *Contraception: Current Principles And Practice*

*J. K. Foster, B.Sc.* 6T9

## INTRODUCTION

The contraceptive problem today remains a topic of discussion in lay and medical publications and, indeed, at every level of society. The indications, methods, and hazards of contraception affect every sphere of Canadian medicine. With increasing public awareness, physicians, both in family practice and in specialized fields, will be required to advise their patients on a choice of contraceptive method. However, in 1966, only 10 out of 12 Canadian medical schools gave at least one hour of didactic lectures on contraception and only six schools exposed their students in small groups to a contraceptive clinic.[1] The graduate of a Canadian medical school in 1968 is inadequately trained to deal with the contraceptive problem. This article will briefly review some principles and the two most recent clinical approaches to contraception.

## SOME PRINCIPLES OF CONTRACEPTION

### A) *General Criteria*

In considering any method of contraception, one must remember three basic axioms proposed by Calderone:

i) *Any* method of birth control is more effective than *no* method.

ii) The most effective method is the one the couple will use with the greatest consistency; therefore, the final choice of method must rest with the patient.

iii) Acceptability to the patient is the most critical factor in the effectiveness of conception control.[2]

Several other criteria must be considered in assessing contraceptive methods: effectiveness and simplicity; safety; reversibility; freedom from side effects; economy.

The term "contraception" as generally used, refers to the *temporary* prevention of pregnancy by various methods, as opposed to the *permanent* prevention of pregnancy by surgical sterilization. We will, therefore, not consider sterilization in this article, and as well, we will omit the *most* effective contraceptive method, abstinence.

### B) *Indications*

Although, in most cases, the indications for contraception are obvious, it is useful to list the current

i) Communal: population control on a world scale.

ii) Individual:

a) mental or physical illness in the husband or wife, or probable defect in the fetus;

b) spacing of pregnancies;

c) inadequate psychic, physical and economic resources of the family;

d) alternative to the undesirable effects of unwanted pregnancy;

e) routine at pre-marital and post-partum visits;

f) patient request, for whatever reason.[3,4]

### C) *Assessment of Effectiveness*

In order to compare the effectiveness of various methods of contraception, a formula devised by Raymond Pearl has been adopted, wherein "R", representing the pregnancy rate per hundred women-years exposure to conception is derived:

$$\text{Pregnancy rate (R)} = \frac{\text{No. of pregnancies x 1200 months (100 yrs.)}}{\text{Total months of exposure to conception}}$$

The pregnancy rate with no contraceptive method is 50 - 100, according to Goldzieher, which means that, of 100 women exposed to possible conception for 1 year, 50 to 100 of these would become pregnant.[5]

Since the effectiveness of any method is the product of the physiologic efficacy of that method and the regularity with which it is used, the pregnancy rate must include both method failure and failure of the patient to use the method in the prescribed fashion. This latter factor may be due to insufficient motivation or to choice of an unacceptable or unsuitable method.

### D) *Classification*

A practical classification of current contraceptive methods has been proposed by Calderone[6] and modified by Guttmacher[7]; they have grouped the non-surgical contraceptive methods on the basis of their theoretical effectiveness. They point out, however, that the theoretical effectiveness is not equivalent to clinical effectiveness, since the latter varies greatly according to the skill and motivation of the clinical population using a certain method. The failure rate or pregnancy rate (R) per 100 women-years exposure, in brackets below, allows comparison of specific methods.[8]

i) Most Effective:

a) oral contraceptive — combined (0.2)
— sequential (1.4)

b) IUCD

ii) Highly Effective:
  a) diaphragm or cervical cap with cream or jelly (12)
  b) condom (14.9)

iii) Very Effective:
  a) aerosol vaginal foam
  b) rhythm method (based on basal body temperature) (14.4)

iv) Less Effective:
  a) cream and jelly alone (20)
  b) foaming tablets (22)
  c) suppositories
  d) coitus interruptus (16)
  e) rhythm
  f) sponge with foam

v) Least Effective: breast feeding period

vi) Probably Ineffective: vaginal douche (plain or with chemicals) (37.8)

Methods grouped in each of the above have approximately equivalent effectiveness. Due to limited space in this presentation, we will examine only the most effective category of current contraceptive practice, i.e. oral contraceptive and intrautérine devices.

## PRACTICAL CONTRACEPTION

### A) *Introduction*

In the past ten years, contraception with oral agents and intrauterine devices has drastically changed the pattern of conception control. They share these features: i) maximum effectiveness; ii) dissociation of the use of contraceptive method and the sexual act itself, leading to; iii) safe spontaneous sexual activity; iv) transferral of contraception control to the female; v) a mechanism of action which is not as yet completely understood.

### B) *Oral Contraceptives*

i) *History:* Oral agents to prevent conception are by no means a modern invention. In the Talmud, reference is made to roots and herbs which when drunk by Rabbi Hiyya's wife prevented further pregnancy. Ancient civilizations employed a wide variety of brews, barks and roots to prevent conception, temporarily or permanently. Synthetic estrogens and progestogens have been used clinically in the treatment of menstrual disorders since 1938. Anima! experiments using these agents as anti-ovulatory compounds were begun in 1954 by Rock and co-workers; Satterthwaite conducted the first human study in Puerto Rico in 1956. The American F.D.A. granted approval in 1960, and since then much experience has been gained. Recently, the dosage of constituents has been decreased to produce minimal side effects while maintaining maximal contraceptive efficacy. Guttmacher estimates between 10.5 and 11.5 million women were using the "pill" around the world in 1966.

ii) *Methods:* Each oral contraceptive product contains one of the potent synthetic estrogens and one of the synthetic progestational steroids, chemically and biologically related to progesterone. The exact composition of various compounds differs, but a commonly used agent such as Norinyl (1 mg) contains norethindrone (1 mg) and mestranol (0.05 mg). Further information on the chemical components of currently used preparations may be found in a recent issue of this journal.[9] There are two basic types of oral contraceptives, combined and sequential. In the combined type of pill, estrogen and progestogen are given concurrently, beginning on the fifth day of the menstrual cycle, day one being the first day of menstrual flow. It is taken at the same time each day for the subsequent 20 - 22 days, depending on the product. About 72 hours after taking the last pill withdrawal bleeding occurs, and the patient begins the next cycle of pills on the fifth day after bleeding begins. If no bleeding occurs after taking the last pill the next cycle is begun seven days after taking the last pill. Amenorrhea is one side-effect of the pill, and the patient should be warned that she is not pregnant if she has taken the pill as prescribed. She should continue with the new cycle of tablets. Amenorrhea after two consecutive cycles of therapy should be reported to her physician, who must rule out pregnancy. In order to avoid possible confusion, newer combined regimens have been devised in which the patient takes placebo pills for seven days after the last combined tablet. She then begins the next cycle of pills no matter whether bleeding has occurred or not.

Sequential oral contraception involves administering estrogen alone for 14 to 16 days, depending on the product, followed by an estrogen-progestogen combination for six more days. The first pill is taken on the fifth day of the menstrual period. The sequential pattern more nearly simulates the natural hormonal sequence of the menstrual cycle.

Post-partum oral contraception may be begun on day five of the first spontaneous menstrual period (usually six to eight weeks post-partum) or during the third or fourth post-partum week, since ovulation may precede the first menstruation. Oral hormones may, in low doses, prevent breast milk production by inhibiting prolactin, and therefore should not be used before lactation is established by women who wish to nurse. After milk appears the "pill" may be prescribed for lactating mothers. Lactation alone provides little protection against conception.

The management of the patient on oral contraceptive therapy has been outlined by the W.H.O.[10] Before beginning treatment, the physician should take a history with specific regard to previous or current hepatic, vascular, cardiovascular or renal disease and a familial tendency to mammary or endometrical carcinoma. In addition to a general physical assessment, the breasts and pelvic organs should be thoroughly examined and a Papanicoulau smear taken. After explaining the method to the patient, her questions should be answered, and she should be warned

of possible side-effects. These should be reported, along with any unusual occurrence at the six month return visit. Many Toronto hospitals schedule this first return visit for three months. Every six months, examination of the breast, abdomen, pelvic organs and rectum should be performed, and Papanicoulau smears are repeated annually. Contraindications and management of side effects are discussed below.

It is most important to emphasize that the regimen must be followed rigidly. The likelihood of pregnancy is increased significantly if tablets are omitted on several consecutive days in combined therapy. The hazard is even greater with the sequential method, where omission of a single tablet in the estrogen phase can lead to pregnancy.

The dosage used should be the minimal amount consistent with the effective contraception and fewest side effects. Guttmacher suggests 1 mg of progestogen to be the minimum effective dose, and warns that the level should not exceed 2.5 mg daily. Most preparations available contain the synthetic estrogen, mestranol, in doses of 0.05 to 0.1 mg. Jeffcoate recommends that no oral hormone be continued more than 2 to 5 years, presumably since the effects of prolonged steroid therapy are as yet unknown.

iii) *Mechanism of action:* The exact method of action is a subject of continuing research, but oral contraceptives are presumed to act in the following way:

a) They prevent ovulation by suppressing the luteinizing hormone of the pituitary gland, preventing the mid-cycle LH surge, which normally triggers ovulation. Either the estrogenic or progestogenic component alone is capable of preventing ovulation, but together they have a synergistic effect[8]. The progestogen, in addition, counteracts some undesired side-effects of estrogen, tending to produce less "break-through bleeding" (bleeding while taking the pills) and more consistent "withdrawal bleeding" (bleeding on cessation of medication)[4 11]. It also exerts a diuretic effect.

b) The cervical mucus, which is thin normally, becomes more viscid with combined therapy and inhibits sperm penetration. Sequential therapy however, causes the mucus to remain thin.

c) Reversible endometrical changes to an "atrophic" or early proliferative glandular pattern occur with combined tablets, and are thought to render the endometrium unfavourable to implantation. Sequential therapy has a different effect, resulting in an early secretory endometrial pattern[5].

Sequential therapy thus acts at different sites than the combined method. Ovulation has been shown to occur without subsequent pregnancy on this regimen, leading Ramon-Garcia to suggest that they affect gamete transport or gamete conditioning[8].

iv) *Indications:* Oral contraception is useful when pregnancy *must* be avoided, particularly when there is a grave risk to health. Young women respond well to this method, especially those with menstrual disorders, such as dysmenorrhea, hypermenorrhea and severe premenstrual tension, all of which improve on oral hormones.

v) *Contraindications:* Considerable controversy with respect to contraindications has centered around the problems of thromboembolic phenomena, carcinogenesis, and hepatic dysfunction associated with oral steroids.

Many investigators feel that a *history of thrombotic episodes or the presence of thrombo-embolic disease* constitutes an absolute contraindication. It is known that the oral steroids cause alterations in some hematological tests suggesting hypercoagulability of the blood, specifically an increase in prothrombin time, and levels of fibrinogen, factor VII, VIII, IX and X. However, Guttmacher claims these biochemical changes have no clinical significance. He summarizes the findings of British and American government committees and the WHO thus: "no scientific evidence exists of any causal connection between oral contraceptives and any of the serious side effects charged to them"[7]. He does grant, however, that the question is still unsettled due to the incomplete evidence available at this time. Loraine and Bell concur that there is presently no evidence of an increased incidence of thromboembolism in users of the "pill", but point out that some types of vascular abnormalities are often associated with the use of oral contraceptives — in particular venous thrombosis and pulmonary embolism. But they state that the risk of thrombo-embolism is greater in pregnancy than on "the pill"[12]. Thus, a patient with previous thrombophlebitis, pulmonary embolism, varicose veins or other factors (eg. severe heart disease, polycythemia) which might predispose to thrombophlebitis and embolism, may use this method of contraception, but must be watched closely for vascular changes. Special attention must be paid to any acute pulmonary symptom which develops in these women, even in the absence of symptoms and signs of peripheral thrombophlebitis.

Although estrogens have not been proven to be carcinogenic in humans, a *history of, or suspicion of, malignancy of the breast or reproductive system* is suggested as a second major contraindication to oral contraception. The possibility that malignancy might be exacerbated has been proposed, but the studies to date show no statistical evidence of an increased cervical, endometrial or mammary malignancy[12]. Indeed, some workers find a decreased incidence of cervical cells which are "suspicious for carcinoma". Recent studies indicate that adenomatous hyperplasia of cervical glands, which occasionally occurs with progestogens, does not progress to carcinoma[13]. Thus, there is at present no basis for a connection between cancer and oral contraception but a definite answer requires more years of clinical evaluation. The WHO suggest caution in prescribing oral contraceptives in these patients.

Oral steroids cause reversible alterations of some liver function tests, notably an elevation of BSP retention and

transaminase levels. These are not associated with any visceral liver damage and are of no clinical significance to normal patients, although cholestatic jaundice occasionally occurs. Since gestational steroids are metabolized by the liver, most authors feel that a *history or presence of a hereditary or acquired defect of the liver* is a contraindication to this type of therapy. However, Guttmacher and the WHO committee believe that the only absolute contraindication to oral contraception is the presence of very rare hereditary liver defects — the Dubin-Johnson syndrome, Rotor syndrome; and ideopathic recurrent jaundice. They suggest that cirrhosis and viral hepatitis are not aggravated by the medication, but advise caution in prescribing oral steroids for a patient with liver disease, past or present. Liver function studies and the clinical condition of the patient should be followed closely in these cases, and therapy stopped if evidence of impaired excretory function is seen.

Until further studies are reported, the more conservative approach is likely to be taken and the absolute contraindications will remain:

a) the history of thrombotic episodes or presence of thrombo-embolic conditions;

b) the history, presence or suspicion of malignancy of reproductive system or breast;

c) the history or presence of hereditary or acquired liver disease (especially when excretory function is impaired)[7 10].

Also, oral contraception is undesirable in the presence of *undiagnosed vaginal bleeding*, as the hormones may aggravate the underlying cause of this disorder. *Severe cardiovascular or renal disease* may also be contraindications since fluid retention may occur. This possibility demands caution in the patient with epilepsy, asthma, migraine and hypertension. Generally, one must weigh the possible effects of such therapy against the effectiveness, availability and acceptance of other methods and against the hazards of pregnancy in that patient.

vi) *Side Effects:* The incidence of side effects varies with different authors, but most agree that the incidence decreases with successive cycles of medication. Persistent side effects may be ameliorated by changing the product. In general, sequential therapy has a lower incidence of side effects.

*Nausea* is a common minor side-effect, due to the estrogenic component, which decreases in incidence after two to three cycles of medication. *Breast tenderness* also is seen, due to fluid retention. Both of these conditions sometimes may be altered by use of a product with an anti-estrogenic progestogen (eg. norethindrone). *Weight gain* commonly occurs, due to the anabolic effect of the steroids, fluid retention and an increased appetite. This problem improves with continued use of the medication, but a change to a product without norethindrone or use of a sequential regimen may be helpful. The pre-treatment menstrual pattern may be altered. *Menstrual flow* is lighter in most patients, but in some it becomes heavier (especially with sequential therapy). *Breakthrough bleeding* is a troublesome symptom and may be treated by having the patient take two pills a day until bleeding stops and increasing the estrogen content of the next supply of medication. Persistent breakthrough bleeding calls for endometrial investigations by biopsy or curettage to rule out organic causes. The incidence decreases with successive cycles. In 5% of patients, *amenorrhea* occurs, and may be treated by decreasing the level of progesterone. Amenorrhea is a special indication for the use of sequential therapy. The patient deciding to stop oral contraception must be warned of a possible *delay in the return of ovulation*. Her first post-treatment cycle may be 22 to 60 days in length, but the pattern should return to normal by the third cycle.

Other effects of this induced "pseudopregnancy" state may be listed. a) *Endocrine changes:* PBI levels are increased; 17-ketosteroid levels decrease; and an altered glucose tolerance curve (pre-diabetic) is seen. These changes have no clinical significance, but oral contraceptives should be withheld for two cycles before assessing endocrine function. b) An increased incidence of *vaginitis* (especially of Monilial type) and cervical erosion may occur. c) *Skin Changes:* improvement of acne and occasional facial hyperpigmentation have been reported. d) *Uterine fibroids* may increase in size (low incidence). e) *Depression* and a variable *change in libido* are seen, and may be very distressing to both patient and physician. f) Various *neuro-ocular lesions* leading to altered vision or diplopia occur infrequently but require investigation.

The *effect on the fetus* has been evaluated and there is no evidence of an increased incidence of genetic defects in children of mothers who have used oral contraceptives. Although masculinization of female fetuses by oral steroids has rarely occurred, oral contraceptives should be discontinued if pregnancy occurs.

*Fertility* subsequent to cessation of oral medications is said to be slightly enhanced, and the WHO quote a report that 90% of women stopping the pill were pregnant within six months. There is no delay in the *onset of the menopause,* since this is determined by genetic not hormonal factors[12], but "the pill" may mask the onset of the climacteric.

vii) *Advantages and Disadvantages:* Using the criteria mentioned earlier, we can now assess oral contraception. The advantages of this method are its effectiveness and relative simplicity of use, especially with new packaging methods and the introduction of placebo pills. While the safety of the pills to the mother and fetus are still being debated, most studies indicate no health hazard to patients adequately screened and followed at regular intervals. Reversibility of contraception and most of the side effects, is another asset of oral steroid pre-

paration. The tablets are widely accepted and convenient to take. Disadvantages of the method are seen in the last two criteria: side effects and economy. Those side effects which persist and are not alleviated by changing to another preparation or a sequential regimen compel some women to use an alternative method. Also, oral contraception is fairly expensive (in the cost of the pill and the medical supervision of the patient) although it is within the reach of most North American females. Cost is a more serious problem in developing countries. One obvious disadvantage, with sequential therapy especially, is the hazard of pregnancy if pills are omitted.

C) *Intra Uterine Contraceptive Devices (IUCD)*

i) *History:* Intrauterine contraception has been known for centuries. Camel drivers discovered that insertion of a small stone in each cornu of a camel's uterus prevented pregnancy; this method is still used today in Tunisia and the Sudan. Human use of the IUCD is more recent, dating back to 1878, when stem and spring pessaries were used to prevent conception and induce abortions. In 1930 Grafenberg of Berlin, reported successful contraception with his silkworm-gut and silver intrauterine "silk stars". Although complications were few in his studies, general use resulted in a high incidence of infection and the method was abandoned. In 1959, independent papers by Oppenheimer of Israel and Ishihama of Japan reported large series of successful cases, and clinical evaluation was undertaken on a world-wide scale. Currently, the actual mechanism of action and side-effects of these devices are being studied.

ii) *Methods:* IUCDs are made of a variety of inert materials and are relatively flexible to facilitate insertion. They can be divided into two groups — those which are completely intrauterine, and those which have appendages which traverse the cervical canal. Examples of the completely intrauterine devices are the Birnberg bow, made of inert plastic (impregnated with barium for X-ray visualization) and the Hall-Stone stainless steel ring. IUCDs with appendages that protrude from the cervix include the Lippes loop, a double - S curve made of polythylene: the Margulis spiral, also of inert plastic; and the Zipper nylon ring. These devices all come in various sizes ranging from 25 to 40 mm in widest diameter. The type of device used is a matter of personal preference, but the Lippes loop seems to be slightly more effective and is recommended today.

Insertion of the device may be done at any time, as long as one is certain the patient is not pregnant. Usually, however, the best time is at or just before the end of a menstrual period, so that cervical dilatation is maximal and bleeding after insertion will be less alarming to the patient. Loraine and Bell recommend insertion at 6 weeks post-partum and post-abortion and 8 weeks after Caesarian section[12]. One study[14] reported insertion on the 4th post-partum day without sequelae, but uterine perforation is more likely at this time. The actual procedure can be done in the office and causes little discomfort. The size of device chosen depends on the dimensions of the uterine cavity as determined by a uterine sound. The uterine appendage is trimmed so that it just protrudes from the cervical os, to facilitate examination and removal.

Management of the patient with an IUCD is simpler than with oral contraceptives, but continuing follow-up is essential. A medical history is taken with special emphasis on parity, menstrual history, vaginal discharge, pelvic pain, and abnormal menstrual bleeding. A general physical examination and pelvic examination are then performed, including bimanual palpation to determine the position of the uterus. At the same time, congenital anomalies and the presence of malignancy are ruled out. With a speculum in place, the cervix is examined for erosion or cervicitis and a Papanicoulau smear and specimens of any discharge are obtained. The device is then inserted, the patient being warned of possible crampy menstrual-like pain on dilatation of the cervix. If the patient experiences severe discomfort or syncope, the procedure is terminated. With the device securely in place, the patient is advised that the pain of insertion will disappear within hours (longer in nulliparous patients) and that she can expect some vaginal bleeding for the first 24 hours, and menorrhagia for the subsequent two periods. The patient then should be told how to feel for the appendage, and must be able to detect this at the cervical os. This must be repeated with washed hands every week. Menstrual pads should be examined to detect spontaneous expulsion, which occurs most frequently with menstruation. Again the possible side effects should be mentioned, and any questions answered. Return visits are scheduled for one month, three months, and yearly after that, with specific instructions to report any serious complications immediately. She should return at once if the device is expelled or is palpable at the os. Annual Pap smears should be done.

iii) *Mechanism of Action:* While the physiologic action remains unclear in humans, research in monkeys indicates that the device accelerates the passage of the ovum through the Fallopian tubes and the ovum deteriorates as soon as it enters the uterus[7]. In humans, sperm migration is not impeded. One explanation is that alterations in tubal and uterine mobility caused by this foreign body in the uterus allow the fertilized ovum to reach the uterine cavity before implantation is possible. Southam, however, states that there is no evidence that the device produces pre-clinical abortion or that endometrial changes preclude implantation[15]. Concrete evidence for this mechanism could raise the legal and moral problems of abortion in the future.

iv) *Indications:* IUCDs are of value when effective contraception is mandatory, but oral contraception is unacceptable, medically contraindicated, too expensive or when supplies and adequate follow-up are not accessible. Since it requires only initial motivation and little skill, it is useful in the unreliable or poorly educated patient. The low cost, durability, simplicity and effective-

ness of the method explain its widespread use for population control in developing countries. The parous patient with normal menstrual function and no pelvic pathology is an ideal candidate for intrauterine contraception.

v) *Contraindications:* Intrauterine contraception is contraindicated in patients having: pelvic pathology; menstrual abnormalities; pelvic pain; or possible pregnancy. Since the IUCD is a foreign body in the uterus, certain types of pelvic organ disease may predispose to two serious complications of the method, namely, *hemorrhage* and *infection*. Active pelvic inflammatory disease obviously is one example. Since 50% of those who develop endometritis or parametritis subsequent to insertion of the device have a past history of gonorrhea or septic abortion, these represent relative contraindications. The presence of cervicitis of non-specific or Trichomonal origin is not a contraindication, but should be adequately treated prior to IUCD insertion. Congenital uterine anomalies and tumours of the uterus (eg. uterine fibroids) tend to distort the cavity and lead to more frequent expulsion, menorrhagia and pelvic pain after IUCD insertion, and thus demand other contraceptive methods. *Persisting menstrual abnormalities* (hypermenorrhea and intermenstrual bleeding) and *pelvic pain*, common side effects of this therapy, also constitute relative contraindications since they may be aggravated or may herald unsuspected pelvic pathology (eg. endometrical carcinoma). Investigation and treatment should be undertaken, and intrauterine contraception should not be used until a diagnosis is made. *Suspected pregnancy* is a definite contraindication since the abortion rate with an IUCD is quoted from Kleinman as being 41% of pregnancies with an IUCD in place[12]. Some authors regard *nulliparity* as a contraindication to the IUCD, since in a small uterus the side effects of expulsion, bleeding and crampy pain are common. The possibility of pelvic infection which may lead to sterility is also of significance in a nulliparous patient. In spite of these difficulties, most physicians consider this method suitable for women who have not had children. However, they point out that insertion of an intrauterine device through a non-parous cervix may be painful and difficult, and occasionally may cause syncope.

vi) *Side Effects:* A number of side effects have been described, some of which may only be remedied by removal of the device. In contrast to oral medications, these adverse affects are less frequently affected by changing to an alternate type of IUCD.

The commonest side effects of the IUCD are pelvic pain and abnormal vaginal bleeding, which lead to removal in 7 - 21% of patients who begin this method[15]. *Pelvic pain* is experienced in the lower abdomen or in the low back region and is similar to menstrual pain. Usually the pain only lasts several hours, but may persist for days. Treatment with analgesics is sometimes required. Surprisingly, dysmenorrhea is usually decreased by this device. *Bleeding* may take three forms: a) Post-insertion bleeding; this occurs with most patients and normally subsides after several days. b) Intermenstrual bleeding; metrorhagia is frequent, but usually does not persist beyond three months. c) Menorrhagia; heavy or prolonged menstrual periods are normal for the first two cycles after insertion. Persistent bleeding is an indication for removal of the device, but sometimes changing to a larger loop is effective. While 50% of women experience bleeding immediately after insertion, only 20% note persistent hemorrhage. Pain and hemorrhage some months after insertion may herald expulsion of the device.

*Expulsion* of the device is an important side effect seen in 10.4% of patients during the first year of IUCD use. This figure decreases markedly after three months of use, and expulsion during the second year of use is only 1.6%. The expulsion rate varies with different types of devices and patients, being generally slightly higher with the spiral-shaped device, smaller sizes of loop, young patients and patients of low parity[2]. Of these expulsions, 20% are unnoticed and many of these lead to pregnancy. In case of expulsion, the device may be reinserted, but only 50% of those replaced will remain in place. Occasionally, a different type of IUCD is better retained. A side effect related to expulsion, and of great significance, is *pregnancy*. The failure rate (R) is 5 pregnancies per hundred woman-years. Two thirds of pregnancies with the intrauterine device occur because of expulsion; the remainder are seen with the device in situ. The incidence of this method failure decreases with increasing years of use. In 2.7% of patients, *pelvic inflammatory disease* occurs with the IUCD[12]. Half of this number have a previous history of gonorrhea or abortion and a greater frequency is seen in lower socio-economic groups. Most of these cases are successfully treated with antibiotics, but the remainder will only clear on removal of the device. Only one-third of these cases are severe enough to warrant hospitalization. The physician must be warned that 15% of patients experience a *transient vaginal discharge* which subsides spontaneously. A rare but serious complication is *perforation of the uterus,* which occurs in 0.2% of cases (Tietze, 1966) — most commonly with the bow type of device. There are usually no symptoms. The danger is greatest in the immediate puerperium. No sequelae occur if the problem is recognized and the device is removed at once.

The suggestion that the IUCD is related to the development of *endometrial or cervical malignancy*, has been studied extensively. While there is no evidence of an increased incidence of endometrial or cervical carcinoma, there are reports of abnormal cervical smears in 2.2% of patients[12]. The cells in these cases were suggestive of carcinoma of the cervix histologically, but most returned to normal within one year of removal of the IUCD. Endometrial cytology reveals an increase in superficial vascularity and local edema, without inflammatory changes. In summary, it can be said that, at this time there is no indication of an increased frequency of premalignant or malignant lesions with this device. Con-

tinued study is necessary, and individual patients must be followed at least yearly.

The IUCD has raised doubt as to adverse *effects on the fetus and subsequent fertility*. There is an increased incidence of abortion if pregnancy occurs with the device in situ, and a relatively high level of ectopic pregnancy (2.5%) in these cases (Tietze, 1966),[12]. There are no complications of labour and delivery and no increase in malformed infants. Fertility after removal of the IUCD is not decreased. The National Council on Maternal Health[15] reports that 87% of those who had the device removed in order to conceive did so within one year. One side effect in the male has been reported, although infrequently — *discomfort during intercourse* due to the cervical appendage.

vi) *Advantages and Disadvantages:* This new method combines great effectiveness, with simplicity of insertion, examination and maintenance, and relative safety. Moreover, it minimizes patient failure in that it requires "once-only" motivation. As greater clinical experience is gained, the acceptability of the method should become more widespread. The major drawback of the IUCD is related to side-effects, which are less significant and dangerous than oral contraceptives, but are more frequent than with mechanical methods (condom or diaphragm).

## SUMMARY

We have thus reviewed some aspects of current contraceptive practice. While concentrating on the newer methods of conception control, we have seen they are not suitable to many couples, and can present serious hazards to health. It is evident that the physician must be aware of the medical, moral, and social aspects of contraception in order to tailor his therapy to best meet the needs of the individual couple involved. The final choice of method must rest with them. It is hoped that the reader will continue to explore this subject in order to adequately meet his commitment to his community.

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SUN LIFE OF CANADA

# *Perinatal Death And Premature Labour*

*H. P. Drutz, B.A.* 6T9

Concern about premature infants has been recorded since Richard III lamented that he was "sent before my time into this breathing world scarce half made up". Prematurity (1000-2500 gm) remains by far the most important cause of perinatal death with an incidence which differs with various ethnic groups and ranges from 70-75 per 1,000 births in white mothers to approximately 150 per 1,000 births in non-white mothers[1]. In the United States prematurity ranks eighth as the cause of death written on all death certificates[2]. Indeed progress in the prevention of premature delivery has been very slow and only in some forty per cent of cases can the cause be demonstrated definitely, with the overall incidence changing very little in the last 20 years. Ultimately the problem is one of interacting multiple variables as they affect the occurrence of what may be considered a disease state. Although only theories exist as to the exact etiology of premature labour, many associated factors have been found to relate the problems of prematurity and perinatal death.

## ASSOCIATED FACTORS

### 1) Complications of Pregnancy

10 to 15% of premature births result from purposeful obstetrical intervention[3], the causes being chiefly maternal: caesarean section, toxemia (toxemia or pre-eclampsia is considered the most common obstetrical complication significantly correlated with low birth weight)[4], abruptio placenta, placenta previa, and pelvic abnormalities. Further causes include diabetes mellitus, rising Rh antibody titre, chronic hypertensive vascular disease, syphylis, acute infections, pyelonephritis, cervicitis, and vaginitis, and a history of previous premature delivery.

### 2) Asymptomatic Bacteria and Urinary Tract Infections

Recent studies have shown that 4.8% of mothers of mature infants show a significant bacteruria (100,000/ml urine) at the time of delivery whereas this occurs in 9.8% of mothers of premature infants[5]. Kass[6] proposes that adequate treatment of asymptomatic bacteruria in pregnancy may decrease the incidence of prematurity; fact has not yet born this out.

### 3) Congenital Defects

Fetal malformations have long been considered a cause of threatened premature labor and chromosomal aberrations are frequently found in products of spontaneous abortions.

### 4) Sex of Infants

Interestingly, it seems as though infants weighing less than 2500 gm are more often female even though all births taken together regardless of weight produce more males[7].

### 5) Single or Multiple Births

Multiple births occur in slightly more than 1% of all pregnancies but 12 to 15% of premature infants are products of pleural births and more than 50% of living infants in multiple births are premature according to weight. Curiously, reports indicate that low-birth-weight infants or products of multiple births have a better chance of neonatal survival than similar infants who are products of single births.

### 6) Parity and Maternal Age

In all countries and ethnic groups the highest prematurity rates are found in primiparas in any age range and mothers less than 20 at each birth order. However, prematurity has been shown to increase in pregnancy after the second and to approach or pass the rate for primiparas in grand multiparas with closely spaced pregnancies[8].

### 7) Socioeconomic Factors

The association of prematurity and lesser affluence is evident when class is measured either by area within a city, by standard of housing, by place of delivery, by standard of maternal care or by ward versus private care[9]. Unwed mothers have been shown to have a prematurity rate no higher than the local community as a whole[10]. The association between working during pregnancy and low birth weight is unclear, just as is the specific relationship between maternal education and personal hygiene, all generally being part of socioeconomic considerations. Taller women tend to have fewer premature babies but are also of generally higher social class.

### 8) Prenatal Care

From the Ontario Perinatal Mortality Study (1967) the incidence of prematurity was four times greater among mothers who received no prenatal care. The perinatal mortality rate varied inversely with the completeness of prenatal care as measured by the number of visits.

It was four to eight times among those with *no* prenatal care than those with *some* prenatal care.

9) Nutrition

The relationship of maternal nutrition during pregnancy to birth weight remains unestablished. However, it is the opinion of most obstetricians that adequate nutrition is one of the most important factors in the prevention of prematurity. The only consistent finding has been a marked increase in the rate of prematurity when the protein intake was less than 50 gm per day.

10) Anemia

A high incidence of prematurity can be shown in anemic women and the more profound the anemia the higher the prematurity rate. Physiologically there is no increase in the cardiac output at rest during pregnancy until the haemoglobin concentration is reduced to about 7 gm/100 ml. Also a strong association can be shown between spontaneous abortion and low serum levels of folic acid. Similarly, relatively conclusive evidence is available today that patients with abruptio placenta (a common cause of purposeful obstetrical intervention or what may be considered iatrogenic prematurity) tend to have folic acid deficiencies[11].

11) Smoking

Infants born to mothers who smoke have significantly lower mean birth weights than those born to non-smokers. Some of the postulated mechanisms are as follows: decreased appetite during pregnancy; nicotine or other components of cigarette smoke produce vasoconstriction which then decreases uterine placental blood supply; a direct toxic effect on the fetus; carbon monoxide of the blood may produce a decreased oxygen-carrying capacity; cigarette smoke may increase uterine contractibility; and smokers are physically or psychologically different from non-smokers.

12) Altitude

Infants born at high altitudes have a lower mean birth weight than those born at lower altitudes. One must take into consideration though that altitude itself is not a simple variable but involves increased cosmic radiation, decreased partial pressure of $0_2$, increased ultraviolet radiation, decreased humidity and decreased temperature as well.

13) Heart Volume and Maternal Weight

Heart volume measurements, in the absence of cardiac disease, reflect the total blood volume, which in turn increases as physical fitness improves. From these considerations evolved the theory that smaller heart volumes might indicate the less biologically fit woman who was then especially prone to premature delivery. A positive correlation was shown between heart volume and maternal weight and, to a lesser degree, maternal height. Heart volume reflected work capacity and insufficient work capacity in pregnancy predisposed to low-birth weight, considered a result of diminished uterine blood flow. Major criticisms now exist to these theories and presently there is stronger evidence that plasma volume is more significantly related to birth weight than heart volume or height and that this relationship holds even when surface area is taken into account[12].

14) Psychologic Factors

Retrospective psychiatric studies of patients with premature delivery have suggested that negative attitudes toward the pregnancy might have been present; however, similar studies of women with complications of pregnancy other than prematurity also implicate psychodynamic factors. The tendency of prematurity and other complications of pregnancy to occur more frequently in lower socio-economic groups suggests that the psychologic attributes of women with abnormal pregnancies are more related to class than a specific psychologic occurrence[13].

15) Miscellaneous Considerations

a) Prematurity rates have been shown to decline in wartime[14]; the explanations given being that either rationing of food may favour the pregnant woman or that lower classes may have better relative nutritional status during wartime.

b) Prematurity has been related to season of birth or conception. Low birth weight infants and births of infants destined to be mentally defective have been reported more commonly in winter and spring[15]. The theory being that summer heat may produce a damaging loss of appetite in the pregnant woman at a critical stage of development of the embryo brain.

## THEORIES ON THE ETIOLOGY OF LABOUR

Since the myometrium is capable of contracting at any stage of pregnancy, it must be assumed that the development of rhythmic contractions is prevented by a mechanism which either inhibits the response of the muscle cells to stimuli, or prevents the stimuli from reaching the cells. It is thought that both these principles may operate in the human. The question as to what exactly removes any safety catches and hence triggers the action presently remains unknown and confusing.

Csapo[16] has shown that progesterone and estrogen alter the ionic distribution across the myometrial cell membrane. Progesterone domination produces low intracellular K and high intracellular Na (opposite from normal). He theorizes that there is an increasing build-up of progesterone between the myometrium and the placental site during pregnancy and that this serves as a "block" to uterine contraction. Removal of this "progesterone block" enables the onset of labour either at term or prematurity. However, it is known that some local unorganized contractile activity does remain (eg. Braxton-Hicks contractions). Also examination of the urinary and blood concentrations of estrogens and progestagens has failed

to reveal any dramatic changes before the onset of labour. The problem remains unsolved.

Caldeyro-Barcia[17] in Montevideo, Uruguay, proposes that Oxytocin is the activating stimulus in labour in the human and several other species. He explains that the blood in pregnancy contains an enzyme, oxytocinase, which inactivates oxytocin before it reaches the uterus. The serum concentration of this enzyme declines before the onset of labour, hence oxytocin is no longer inactivated and uterine contractions begin. Some observations in sheep indicate that the signal for oxytocin release may be provided by the fetus itself. Liggins and Holm[18] have shown that sheep, with fetuses that have been hypophysectomized or adrenalectomized in utero, do not go into labour spontaneously. Since it is the infant that provides the signal for oxytocin release during lactation, it is not unreasonable that the fetus may provide a signal for oxytocin release at parturition.

Amidst these proposals remains the question of what mechanism actually starts the gravid uterus into labour either at term or prematurely.

## THEORIES ON THE TREATMENT OF PREMATURE LABOUR

### 1) Pharmacological

Drug therapy for premature labour attempts either to render the myometrium unresponsive to stimuli or to prevent the release of activating stimulus. The following approaches have been reported:

a) *Progestational Agents:* The failure thus far of progestational agents has not proved in fact that they do not play an essential role in the safety mechanisms of uterine activity on pregnancy. It is possible that the oral and parenteral administration so far used has not provided the myometrium with a sufficiently high and constant level of progestagen. Fuchs[19] calculated that if the myometrium is dependent upon a progesterone concentration of the same magnitude as that in the uterine venous blood in normal pregnancy, the uterine artery would have to bring blood to the uterus with a concentration 9 - 10 times higher than normal, were the placental progesterone production to be substituted. This would require a constant I.V. infusion of 1350 - 1800 mg of progesterone in mid-pregnancy and 2 - 3 times as much toward the end of gestation. This is obviously not practical and what is needed is a synthetic progesterone with a much longer half-life in the circulation and/or a greater effect on the human myometrium.

b) *Isoxuprine:* This is a synthetic adrenaline-like substance which is known to inhibit myometrial activity under certain circumstances. The principal side effects are tachycardia and hypotension which are mediated via the $\beta$ adrenergic receptors. Myometrial inhibition is a papaverine-like action. It has been given orally in doses of 30 mg Q. I. D.[20] and presently seems to have limited effect.

d) *Ethyl Alcohol:* Anna Riitta Fuchs[21] has shown that the inhibition of the release of oxytocin from the posterior pituitary gland can be achieved in the rabbit by administration of ethyl alcohol. By such treatment the milk ejection reflex could be blocked and the onset of spontaneous parturition postponed. Similar results were obtained in lactating women. In all these experiments it appeared that the mammary glands and the uterus remained sensitive to exogenous oxytocin during alcohol administration, showing that the effect of alcohol must be central in the release of oxytocin, rather than peripheral on the response of the target organs. On the basis of these experiments alcohol was given I.V. to women in threatened premature labour in order to see whether inhibition of the release of oxytocin would stop the uterine contractions in labour. Results[22] were promising. However, alcohol is not devoid of general side effects and it is possible that the release of oxytocin is more difficult to inhibit in persons accustomed to the use of alcohol. A substance acting selectively on the release mechanism would be desirable — a challenge to pharmacology.

e) *Oxytocin-Antagonists:* If the receptor sites on the myometrial cells were already occupied by a non-oxytocic substance labour would be prevented. Presently much work is being done to find octapeptides and related compounds with affinity to the receptor sites, but devoid of oxytocic and adverse physiological properties.

f) *Relaxin:* This polypeptide hormone has been isolated from the corpus luteum with the specific capacity to relax the symphysis pubis of guinea pigs, gophers and mice; and it is active only when injected into an animal in esterus. It has been reported as postponing the onset of true labour in threatened premature delivery[23]. The evidence is not yet conclusive.

### 2) Surgical

a) *Shirodkar's Operations:* In cases where threatened abortion or premature delivery have been attributed to incompetence of the internal os of the cervix this procedure has been used[24].

## CONCLUSIONS

Prematurity remains the commonest cause of perinatal death. Although many associated factors have been presented little is known about what actually causes the gravid uterus to begin contracting in a labour-like pattern before the fetus has reached term. Hence the problem of premature labour remains a challenge: a challenge to the physiologists and endocrinologists to discover the underlying mechanisms; a challenge to the pharmacologist to discover adequate therapy; and a challenge to the modern obstetrician to improve its management and eventually lower its incidence. Perhaps the query, "are

these prematures worth saving?". Such arrogance need only be answered by considering that such men as Newton, Darwin, Voltaire, Napoleon, Renoir, Hugo, Churchill, and the author — were all premature.

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# *Rheumatic Valvular Heart Disease In Pregnancy*

*P. Mohide* 6T9

## INTRODUCTION

Heart disease ranks high in the list of causes of maternal death and morbidity in pregnancy and the postpartum period. It is a difficult and unrelenting adversary and requires the most thoughtful and active preventive, medical and/or surgical therapy. Most of all it must be identified early in pregnancy. The pregnancy must be carefully planned with balanced consideration of those factors affecting the prognosis for medical and surgical treatment, the advisability of abortion, and the special problems associated with labor, delivery and the postpartum period.

With any degree of serious heart disease there is no place for single-handed management. The approach to the patient must be coordinated between the family physician, the cardiologist, the obstetrician, and the anaesthetist. Proper use must also be made of other paramedical personnel whose assistance may be invaluable.

## INCIDENCE

Heart disease affects 2% of all pregnancies, and in 90% of these cases the heart lesion is of the rheumatic valvular type. The remaining 10% suffer from a variety of cardiovascular conditions such as congenital, hypertensive, arterio-sclerotic and luetic disease. Although the general incidence of heart disease in pregnancy has not changed for many years, there has been a relative increase in the number of pregnant cardiac patients carried to term. This is in part due to better control and decreased incidence of infections, anemia, and toxemia in pregnancy.

Among those suffering from rheumatic heart disease the mitral valve is affected in 70-80% of cases and almost all of these cases are mitral stenosis. In another 10 - 15% of cases both the mitral and aortic valves are affected.

The overall mortality for heart disease in pregnancy is about 1%, and in this 1% most started their pregnancies with quite severe heart disease. Chesley (March 1968) points out in his 26-year follow-up study of 1,500 successfully pregnant cardiac patients, there is no evidence that pregnancy, once completed, affects the overall prognosis for the patient's heart disease.

## PHYSIOLOGY

A clear knowledge of the physiological changes which occur during pregnancy and the way in which they affect the diseased heart is essential. The special problems of diagnosis and management are much smaller with a clear understanding of what is happening.

### A—Cardiovascular

Starting at the beginning of the second trimester cardiac output increases progressively until it reaches a maximum of about 30 - 50% above normal by the 28th - 30th week of pregnancy. There is still some controversy about changes in the last month. Some investigators believe that cardiac output decreases to 15% above the non-pregnant normal level; others insist that there is a plateau and no decrease. However, it is clear that cardiac reserve does tend to increase in the last weeks.

Stroke volume increases, as does pulse rate; pulse increases to about 88 beats per minute by 34 - 36 weeks. That is 14,000 extra beats per day.

Changes in blood pressure are slight. Systolic blood pressure does not change. There is a small drop in diastolic pressure, due to decreased peripheral resistance, which is maximum at 7 - 8 months. The pulse pressure is thus widened. During the last month of pregnancy these pressures return to normal non-pregnant levels.

Venous pressure is unchanged in the upper extremities but it is raised in the lower extremities. This is probably due to a combination of factors which include the pressure of the gravid uterus on the pelvic veins, the increased uterine blood flow into the venous system, changes in body water, hypervolemia and to some extent cardiac decompensation.

Circulation time is increased. Part of this may be due to the placenta which acts as a large A-V fistula. The low resistance of the uterine sinusoids permits large volume of blood to flow with relative ease from the arterial to the venous system. This results in a decrease in peripheral resistance and a decreased arterio-venous oxygen difference. To compensate cardiac output increases. It has been postulated that the return of cardiovascular parameters to normal non-pregnant levels in the last weeks of pregnancy may be due to the gradual senescence of the placenta which gradually closes off these A-V anastomoses and thus shuts off the functional fistula.

These changes in blood volume, stroke volume, pulse rate, pulse pressure, circulation time all act to increase cardiac work and cardiac output. This increased activity decreases the heart's ability to respond to additional stress. Indeed in one-quarter of pregnancies at about 25 - 35 weeks there is sufficient cardiac decompensation to yield a significant rise in right ventricular and diastolic pressure. It is thus easy to see that a diseased heart with impaired function is even less able to handle this extra work load.

### B—Respiratory

Oxygen consumption rises 10 - 25% however; minute ventilation increases out of proportion to this increase. This "overbreathing" leads to a decrease in $pCO_2$ and a tendency to dyspnea on mild exertion. Inspiratory capacity increases while expiratory reserve volume decreases. Vital capacity and maximum breathing capacity are usually unchanged although vital capacity may increase somewhat. The respiratory and cardiovascular load of pregnacy has been compared to mild physical exercise 24 hours a day.

### C—Hematological

Blood and plasma volumes increase by 20 - 40% in the period from 13 - 32 weeks. There is a drop in volume in the last weeks before term. The total number of red cells increase but not as much as the plasma volume so that haemoglobin and hematocrit values fall. Blood viscosity decreases. The ESR starts to rise at the 24th week and may even go as far as 100.

### D—Metabolic and Endocrine

Total body water and sodium rise to 20% above non-pregnant levels by term. This is probably due to sodium retention and a decreased GFR perhaps largely due to the effects of progesterone and estrogen. Serum proteins, especially albumin, are sharply decreased. Plasma anions and cations are decreased by about 5 meq/l. Plasma osmotic pressure falls. Aldosterone levels rise after the first trimester perhaps secondary to progesterone's naturetic effect, and drop rapidly to normal after delivery. The levels of ADH do not change but a significant anti-ADH activity has been demonstrated in the serum of pregnant women[6 7].

If there is any liver damage secondary to congestive heart failure, there may occur a decreased rate of estrogen inactivation and thus an increased blood level of estrogens. Furthermore, a placental growth-hormone-like substance has been demonstrated which lowers GFR and RPF and leads to sodium and potassium retention[8].

### E—Labor and Delivery

The degree to which the cardiovascular system is stressed in pregnancy is similar to the extra load during moderate physical activity. Congestive heart failure is rarely found during labor and delivery because the work load at this time is often less than the load in the month before delivery and the post-partum period.

During contractions cardiac output increases 20 - 30% and the pulse rate and blood pressure also rise. Between contractions the pulse rate should never exceed 110 beats per min. During the third stage of labor cardiac output and left ventricular work rise due to an increase in venous return. This is due to release of uterine pressure on the inferior vena cava and later to the draining of the uterine sinusoids.

## CLASSIFICATION

I Patients with heart disease but without symptoms or without limitation of their physical activities.

II Patients with heart disease which limits their activities by causing symptoms of dyspnea, pain, palpitation, or fatigue on normal exertion.

III Patients with heart disease which severely limits their activities.

IV Patients with heart disease who can carry out no physical activity without discomfort.

Greater than 70% of pregnant cardiacs are in class I and less than 5% are in classes III and IV.

## DIAGNOSIS

This may be very difficult especially with class I and II patients. The list of abnormal signs and symptoms which may be present in normal healthy pregnancy is long. Dyspnea, hypertension, syncope, and leg edema are frequent. Heart volume is normally increased 10 - 15% and the heart is displaced upward and laterally such that cardiomegaly may be misdiagnosed. Compression of the lower segments of the lungs may lead to fine basilar rales.

There are also many changes in auscultation which occur. There may be a functional systolic murmur, a systolic bruit from the mammary artery or a venous hum from the large mammary veins. The first sound may be split, and there may be a loud third or fourth sound. Early diastolic murmur may be harmless but a diastolic murmur is usually a good indication that cardiac disease is present. There may be E.C.G. changes which include left axis deviation late in the third trimester, inverted T waves, deep Q's, ST segment depression, and low QRS voltage.

Clearly there are many traps laid for the enthusiastic diagnostician. There are however signs which strongly indicate the presence of heart disease. Some of these are a diastolic murmur, clear cardiomegaly, a systolic murmur greater than or equal to a grade 3/6, severe arrhythmias, friction rubs, true angina, diastolic gallop rhythm, pulsus alternans, persistant bacteremia or rib-notching on X-ray.

## COMPLICATIONS

The greatest causes of mortality in pregnant cardiac patients are congestive heart failure and acute pulmonary edema (65% of all mortality). The incidence of these complications closely parallels the increases in cardiac output and blood volume. The incidence is greatest in the eighth lunar month of pregnancy and from 24 - 76 hours in the post-partum period. Subacute bacterial endocarditis and pulmonary embolism are also important causes of maternal mortality.

The most common serious complication is pre-elamptic toxemia which occurs in 10% of these patients. When this occurs, the cardiovascular system is called upon to respond to the additional stress of hypertension and increased hypervolemia. It is not surprising then that this complication can rapidly lead to heart failure and a life-threatening situation. Its prevention and control are thus of paramount importance.

Anemia (< 11gm%) is present in one-third of patients and is of the iron deficiency type in virtually all cases. Other important complications to be avoided are chest infections, pyelitis, leg vein thrombosis, persistent resistant sinus tachycardia and subacute bacterial endocarditis of the puerperium. Another interesting but rare cause of mortality is post--partum heart failure which appears to be a reversible toxic degeneration of the myocardium. Recovery without residium is the rule but takes many months.

## MANAGEMENT AND THERAPY

### *General Objectives*

The maintenance of adequate cardiovascular function is very important. The system must be protected from any abnormal stresses such as toxemia, anemia, arrhythmias, obesity, hypertension, infections (especially of the lung), and excessive physical or mental strain. Signs of left or right-sided congestive failure must be dealt with effectively and with some urgency. Heart failure occurring in the first trimester may face the physician with an important decision, whether or not to continue the pregnancy.

## MEDICAL TREATMENT

The earlier in pregnancy that the cardiac patient can be identified and assessed the better. The special problems of diagnosis and evaluation of heart signs in pregnancy have already been discussed but it is important to point out that these problems increase as pregnancy progresses. The patient should be seen frequently throughout the pregnancy and most suggest that the patient should be hospitalized if signs of heart failure occur. In any case, a hospital delivery is absolutely mandatory. Cardiological, obstetrical and surgical consultations should be made before any special problems arise. The heart patient has a right to the most enthusiastic application of all the talents of her entire medical team.

Therapy for class I and II patients consists largely of control of exercise and diet. The patient should be encouraged to have a housekeeper and to avoid all excessive physical effort (e.g. climbing sairs). She should get plenty of sleep and should not have outside employment during the period of her pregnancy. These factors must be stressed even more strongly in the third trimester. If the patient is overweight she should be encouraged to lose weight and also be told to avoid excess salt and fluid in her diet. If fluid retention or observable edema is present the patient should be started on 25 - 50mg hydrochlorthiazide per day in divided dosage.

Class III patients require more restrictive measures. Activity must be markedly reduced encouraging bed rest and quiet sitting. If evidence of heart failure is found the patient should be restricted to bed rest and sitting in a chair. If the failure is persistent the patient should be hospitalized. A low sodium, reduced fluid diet should be strictly adhered to. The patient should be given diuretics and certainly if there is failure she should be digitalized; however, many feel that prophylaxis is in order if there is a history of congestive heart failure, any significant cardiomegaly, or if examination and tests reveal a tight mitral stenosis. Digitalization should be conducted slowly in order to protect the fetus. It may be conducted more rapidly if acute failure occurs.

Class IV patients should, of course, have the complete regimen of total bed rest, low sodium, reduced fluid diet, diuretics and digitalis. If the patient is class IV in the first trimester a therapeutic abortion must be very seriously considered.

Acute pulmonary edema must be watched for. If the patient has dyspnea at rest, nocturnal dyspnea, or congestive râles, this should be taken as warning of the onset of acute pulmonary edema. She should be put on immediate bed rest, digitalization, fluid and salt restriction, diuretics and oxygen. However, one may be faced with frank pulmonary edema with acute dyspnea, orthopnea, wheezing respiration, frothy blood-tinged sputum, cough, cyanosis and moist bubbly râles. This should be treated as any case of acute pulmonary edema with oxygen, morphine, rotating tourniquets, digitalis, diuretics, aminophylline, phlebotomy and antibiotics as indicated.

## THERAPEUTIC ABORTION

10% of all therapeutic abortions are performed because of heart disease in pregnancy. The risk of failure is least when conducted in the first trimester, and probably is contraindicted beyong 16 - 20 weeks. Thus, an early decision must be made about the patient's prognosis and the advisability of abortion. This must be decided on the basis of many factors: the severity and activity of the disease, the age of the patient, the history of past failure and success of past medical management.

Therapeutic abortion is not indicated in mild class I and II and most of class III patients. Even the moderately severe cases can be carried without difficulty; however, severe advanced disease may be an indication for abortion.

Therapeutic abortion from the second trimester onwards is considered dangerous; an abdominal hysterotomy is required which entails greater risk of infection, thrombo-embolism, heart failure, shock and hemorrhage. The risks of continued medical management must be

carefully balanced against the risks of this procedure. Usually it is better to continue the pregnancy than to face these risks.

## SURGERY

The modern techniques of closed and open heart surgery offer the attending physician an alternative to therapeutic abortion in managing the severe cardiac patient in pregnancy. The decision whether or not to engage in surgery is very difficult. Both closed and open heart surgery are major surgical procedures with considerable risks attached. It is generally agreed that it is preferable to carry the patient through pregnancy and then operate if indicated in the non-pregnant state. If surgery is to be performed it must be done as early in pregnancy as possible.

The operation most often considered is a mitral valvulotomy for mitral stenosis. This is a closed-heart procedure. Of course severe heart disease in the first trimester would normally be an indication for therapeutic abortion; but, for instance, if the patient is a primipara, who has had difficulty conceiving, and who also has severe mitral stenosis and wants the baby, then a mitral valvulotomy should be considered[11]. This type of surgery might also be considered in cases where severe intractable pulmonary congestion occurs early in pregnancy in a woman who refuses to have her pregnancy interrupted or if the same occurs after unsuccessful, enthusiastic medical management after the fourth month when therapeutic abortion is also a high risk procedure[11].

Procedures to correct PDA's, coarctation, and pulmonary stenosis have also been performed infrequently. Patients with aortic insufficiency and septal defects usually tolerate pregnancy well. On the other hand, patients with severe aortic stenosis or mitral insufficiency are at high risk and should have therapeutic abortions.

## LABOR, DELIVERY AND THE POST PARTUM PERIOD

For mother and child this is a most critical period. It is here that a detailed knowledge of process, drugs and procedures and enthusiastic attention to detail are rewarded by a successful delivery and a healthy mother and child. The penalties for ignorance or carelessness in this period are severe and include SBE, circulatory collapse, shock after moderate or severe blood loss, immediate post-partum heart failure (due to transient hypervolemia), hypotension due to inappropriate anesthesia and post-partum septicemia.

Heart disease is not an indication for premature delivery or Cesarian section; since both of these increase the risk and stress associated with labor and delivery. The only indications of these procedures are obstetrical.

Of these pregnant cardiacs who come to term the majority will start labor spontaneously and deliver without the necessity of medical or obstetrical intervention. Forceps are indicated for delay in stage II or with symptoms of dyspnea, chest pain or other signs of failure, but most obstetricians routinely apply forceps at low pelvic station and this seems a reasonable attempt to minimize stress and blood loss.

If there is an obstetrical reason for Cesarian section the risks of this procedure must be carefully considered. It adds stress and presents the risks of infection and greater blood loss. There are also risks of prolonged anesthesia and the post-operative risk of thromboembolism. However, heart disease is not a contraindication to section as long as there is a strong, valid obstetrical indication.

Special attention must be given to aseptic technique because of the risk of bacterial endocarditis. In addition prophylactic penicillin should be started 1 - 2 hours prior to delivery and continued for at least 2 months. Oxygen by nasal catheter or face mask should be given to those with a recent history of failure or to those in significant respiratory distress. If the patient is not already digitalized digoxin and diuretics should be started prophylacticly if one is at all worried about cardiac function during or after delivery.

The particular form of anesthesia used is less important than the skill and judgement of the anesthetist. He must be experienced and well acquainted with the special problems posed by the pregnant patient with heart disease. Inhalation anesthesia is safe provided the patient is adequately prepared, has an empty stomach and has been well premedicated. The risk of hypotension when using spinal anesthesia may be great in inexperienced hands; however, this procedure may be perfectly safe in the hands of a highly competent anesthetist. Local pudendal and perineal block may also be used.

In the post-partum period uterine atony may occur posing the threat of considerable blood loss. This is an indication for the use of Pitocin. If shock occurs whole blood should be used; otherwise, intravenous infusions should be avoided. Early ambulation following delivery should be stressed as prophylaxis against thromboembolism.

Because of the danger of heart failure due to hypervolemia, bacterial endocarditis, toxemia and uterine sepsis the patient should be kept in hospital under observation and on reduced activity for two weeks following delivery.

## SUMMARY

The special problems associated with the occurrence of heart disease in pregnancy have been discussed. The need for detailed understanding of the special intricacies of physiology, diagnosis and management have been stressed. In most cases, with enthusiastic application of the principles and procedures described above the prognosis for a successful pregnancy is good.

*(Continued on page 99)*

# *Toxemia Of Pregnancy - Prevention And Management*

*P. Fitzsimmons, B.Sc.* 6T9

Toxemia of pregnancy merits consideration by all physicians concerned with the welfare of pregnant women. The incidence of pre-eclampsia is 1.5% in private patients and approximately 12% in clinic patients; the average perinatal mortality is 5 - 9%. The incidence of eclampsia is approximately 0.07% of all deliveries; the perinatal mortality is approximately 22% and the maternal mortality is 3 - 10%.

Intelligent management of toxemia requires familiarity with its etiology and pathogenesis. The specific etiology of toxemia is unknown although a number of theories have been proposed. The uterine ischemic theory is supported by experimental evidence. The pregnant uterus and its contents require an increasing blood supply but in toxemic patients uterine blood flow may be decreased by 40 - 50%. Investigators have put rigid metal rings around the uterine and ovarian vessels of non-pregnant animals which resulted in chronic ischemia of the uterus and its contents. The typical picture of pre-elampsia developed.

It is proposed that placental ischemia leads to formation of a pressor substance which contracts renal arteries and may activate the renin-angiotensin system. Such a substance, either angiotensin II or an angiotensin-like substance, may have been recently discovered in the decidua and placenta of toxemic patients[2].

De Alvarez[3] describes the pathogenesis of toxemia as follows: initially, attenuation of the renal interlobular, afferent, and efferent glomerular arterioles (probably due to a vasoconstrictor substance released from the ischemic uterus) reduces the glomerular filtration rate and renal blood flow. Necrosis and hemorrhage occurs in the glomerular capillaries and tubular cells. With the drop in renal blood flow, vasopressors are released from the kidney, resulting in augmentation of the angiospasm. The resultant anoxia causes an increased capillary permeability through histotoxic changes. These effects promote sodium and accompanying water reabsorption. The total extracellular fluid volume is increased. The edema is first localized and then becomes generalized due to further aggravation of capillary permeability. The generalized edema may result in the following sequelae: pulmonary edema; increased cyanosis due to decreased oxygen carrying capacity and oxygenation; left ventricular failure, accompanied by decreased pulse pressure and increased heart rate, due to increased total blood volume and cardiac load.

All of the clinical signs and symptoms of toxemia are adequately explained by abnormal sodium retention and generalized vasconstriction as shown in diagram below.

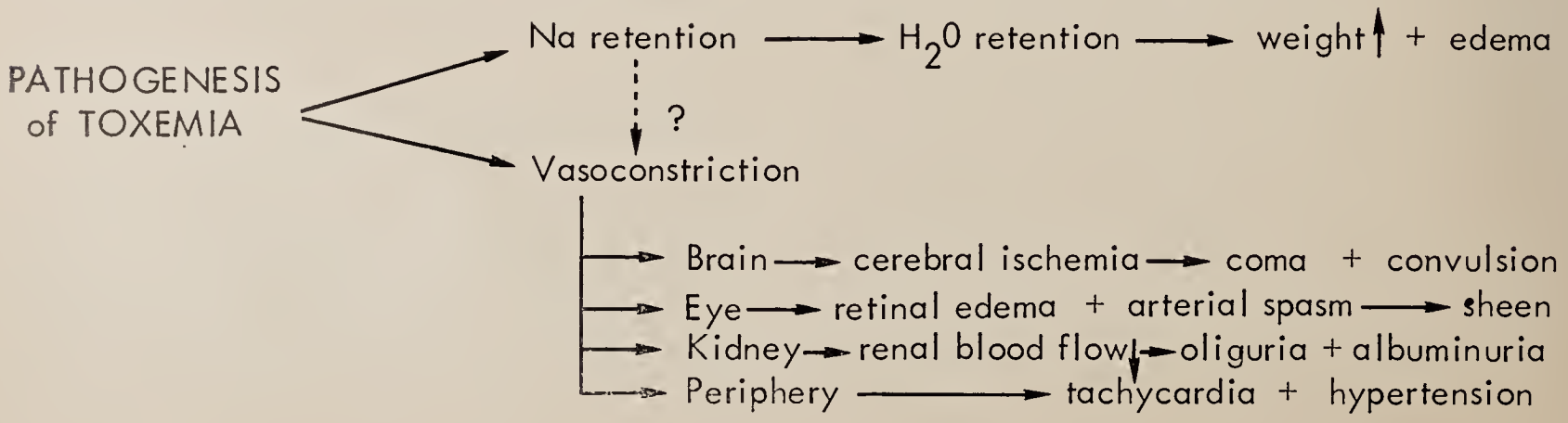
The management of toxemia of pregnancy is directed toward reversing the physiologic abnormalities noted above, chiefly, sodium retention, from which the other abnormalities evolve.

### Prevention of Toxemia

Clinically it has been observed that sodium retention usually precedes generalized vasoconstriction. If sodium retention is prevented, in most cases vasoconstriction will not occur. Early prenatal care is imperative. All foods high in sodium are restricted from the beginning of pregnancy. No limit is placed on fluid intake. Brewer[4] suggests that toxemia is a catabolic disease due primarily to poor protein intake and recommends the use of protein supplements of 100 grams or more, per day.

### Management of Mild Pre-eclampsia

Mild pre-eclampsia is defined as the presence, after the 20th week of pregnancy (and due to the pregnancy itself) of at least two of the triad of edema, elevation of blood pressure, and proteinuria where the average elevation of blood pressure is 40/20 mm. Hg above the non-pregnant level, or if the pressure is between 140/90 and 160/100; the proteinuria is less than 5 grams per day; the daily urine output is greater than 500 ml.; and generalized edema and pulmonary edema are absent.


PATHOGENESIS of TOXEMIA
Na retention
$H_2O$ retention
weight ↑ + edema
?
Vasoconstriction
Brain → cerebral ischemia → coma + convulsion
Eye → retinal edema + arterial spasm → sheen
Kidney → renal blood flow ↓ → oliguria + albuminuria
Periphery → tachycardia + hypertension

As noted, the toxemic process consists of two phases: an early phase, where sodium is retained, plasma volume is increased, and hematocrit is decreased and a late phase where sodium is retained and there is generalized vasoconstriction with a decrease in plasma volume and increase in hematocrit. The thiazide diuretics have proved to be invaluable in the treatment of the early phase. The basic disease process is altered. Sodium is eliminated; the hematocrit rises; and plasma volume falls. Thus, the hemodynamic state is returned to normal and the toxemic process is reversed. However, the thiazides given in the late phase after *sodium retention and generalized vasoconstriction* have occurred are ineffective or even harmful, since they may decrease the already reduced plasma volume and increase the hemoconcentration. Finnerty[5] advocates the prophylactic use of the thiazides in patients especially prone to toxemia — those with chronic hypertension, renal disease, diabetes or young primigravidas — since it is difficult for patients to remain on a low salt diet. The thiazides may be given to most patients continuously without encountering drug resistance. At the first sign of sodium retention diuretic therapy (e.g. hydrochlorothiazide 50 mg. b.i.d. is initiated). Dietary sodium restriction is not necessary in such a regimen. If edema has not been reduced in one week, acetazolamide 250 mg. b.i.d. every three or four days may be added. The mild pre-eclamptic, if her condition remains stable or improves on therapy, does not require hospitalization or sedation. Thus, mild pre-eclampsia may be palliated but cure is not achieved until the patient has delivered.

### Management of Severe Pre-eclampsia

Severe pre-eclampsia may be defined as was mild pre-eclampsia except that the hypertension is greater, with a 60/30 mm. Hg. elevation over non-pregnant state or pressure higher than 160/100; proteinuria exceeds 5 gm/24 hours; urinary output is less 500 ml/24 hours. In addition, visual or CNS disturbances or hyperactivity may be present. There may be massive generalized edema or pulmonary edema. The severely pre-eclamptic patient has entered the late phase of the toxemic process. The following alterations in physiology have ensued:

1. Sodium retention has occurred.
2. Generalized vasoconstriction — especially vasospasm of the arterioles which reduces the blood flow to uterus and placenta and thus compromises the fetus — has followed sodium retention.
3. Increased CNS irritability is evident. Reflexes are hyperactive.
4. Renal function is impaired. GFR is down. Oliguria is noted in severe pre-eclampsia.
5. Hemoconcentration has ocucrred; blood volume approximates that of a non-pregnant patient whereas in normal pregnancy it is 1000 cc greater.
6. The patient is in negative nitrogen balance (i.e. catabolism).

As in the management of mild pre-eclampsia, treatment must be directed towards reversal of the altered physiology. The patient must be hospitalized with bed rest in order to increase blood flow to the ischemic uterus and kidneys. Low salt diet is given. Intake and output are recorded and the patient should be weighed daily to assess the effect of therapy in promoting diuresis. Mild sedation such as 30 mg. of phenobarbital q.i.d. is used to make bedrest more acceptable and to reduce central nervous system irritability. Specific hypotensive agents are not required unless the patient is in danger of a cerebrovascular accident (if blood pressure exceeds 200/130 or if toxemia is superimposed on previous hypertension). If the reflexes are markedly hyperactive, intravenous magnesium sulphate (10 - 20 gm. in 1000 cc of 5% D/W) may be used at the rate of 1 gm per hour; frequent testing of the reflexes is necessary. The state of hydration is assessed by serial hematocrits and urine specific gravities. Improvement, heralded by diuresis and slight drop in blood pressure, should occur within 24 - 48 hours. Magnesium sulphate may then be decreased or stopped. If diuresis doesn't result in a weight loss of 2 Kg. in one week, thiazide diuretic may be tried. If the patient is at 34 weeks of gestation or more, she should be induced and delivered vaginally. No patient with toxemia, even if her symptoms are well controlled, should be allowed to go past term.

### Management of Acute Eclampsia

Elampsia may be defined as severe pre-eclampsia plus convulsions or coma due to the presence, or influence, of pregnancy.

In the eclamptic patient, as in all convulsive and comatose states, maintenance of an adequate airway is essential. During a convulsion a padded tongue depressor may be used to prevent self-injury of the mouth and tongue. After a convulsion, an airway should be inserted and suction applied as required to prevent aspiration. Oxygen therapy may be beneficial.

A convulsion may be stopped by giving 4 - 6 gm of magnesium sulphate intravenously over five to ten minutes. Intravenous sodium amytal is also useful (500 mg or more). Control of imminent convulsions is attained by giving a loading dose of 2 - 4 gm of magnesium sulphate followed by magnesium sulphate infusion at the rate of 1 gm per hour[6]. Exact dosage is decided upon by monitoring urinary output (via a Foley catheter), the knee jerks, and the respiratory rate. Since magnesium sulphate is excreted only by the kidney, urine output must be at least 30 ml per hour or the dose of magnesium sulphate must be decreased. Reflexes and respiration should be checked frequently. The major action of magnesium sulphate is central nervous system depression, and toxicity is indicated by absent knee jerks and a respiratory rate of less than 14 per minute. Cardiac arrest can occur in overdosage. Calcium gluconate (an ampoule of which should



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†Robert Burstein, MD, St. Louis, JAMA, Oct. 30, 1967. Vol 202, No 5.

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**CLINICAL EXPERIENCE:** ORTHO-NOVUM SQ has proven highly effective in the control of conception and menopausal symptoms.

Almost all patients using ORTHO-NOVUM SQ tend to have a regular menstrual cycle with practically no change in amount of flow. Weight change is insignificant.

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**PRECAUTIONS AND CONTRAINDICATIONS:** Although no causal relationship has been proven between the use of progestin-estrogen compounds and the development of thrombophlebitis, physicians should be cautious in prescribing ORTHO-NOVUM SQ Tablets for patients with thromboembolic disease or a history of thrombophlebitis.

Patients with pre-existing fibroids, epilepsy, migraine, asthma or a history of psychic depression, should be carefully observed. Pretreatment examination should include a Papanicolaou smear.

ORTHO-NOVUM SQ should not be taken: In the presence of malignant tumors of the breast or genital tract: In the presence of significant liver dysfunction or disease: In the presence of cardiac or renal disorders which might be adversely affected by some degree of fluid retention: During the period a mother is breast-feeding an infant.

**PACKAGING:** ORTHO-NOVUM SQ tablets are available in DIALPAK* Dispensers (one cycle of use).

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be at the bedside) given intravenously reverses the toxicity.

Fluid balance should be maintained by measuring daily urine output, adding insensible loss, and replacing this total volume with 5% D/W. Hematocrits and urine specific gravity, and protein content, every 6 - 8 hours, as well as daily serum electrolytes and blood urea nitrogen are essential aids to the clinical assessment of the patient's renal and circulatory status. Because aspiration pneumonia commonly occurs in eclamptic patients, a portable chest X-ray should be done after a convulsion. Hypotensive agents are used only to prevent a cerebrovascular accident. Decreased blood pressure decreases uterine blood flow and compromises the fetus.

Delivery of the patient is the definitive cure of toxemia. Any patient who has convulsed, regardless of her period of gestation, must be induced (rupture of membranes and oxytocin drip) and delivered as soon as her condition is stable. This is usually 6 to 14 hours after a convulsion. Uterine activity is increased in eclampsia, so little difficulty is encountered in induction although occasionally a Caesarean section is required. Each case should be considered individually and maternal welfare should be the primary concern of the attending physician.

In summary, the current concept of etiology and pathogenesis of toxemia has been briefly discussed and a method of management has been suggested for the prevention of toxemia, ,the treatment of mild and severe pre-eclampsia, and acute eclampsia.


*ACKNOWLEDGEMENT*

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# *An Introduction Into The Use Of The Colposcope In The Diagnosis Of Cervical Lesions*

*P. M. Blachford* 6T9

## HISTORY

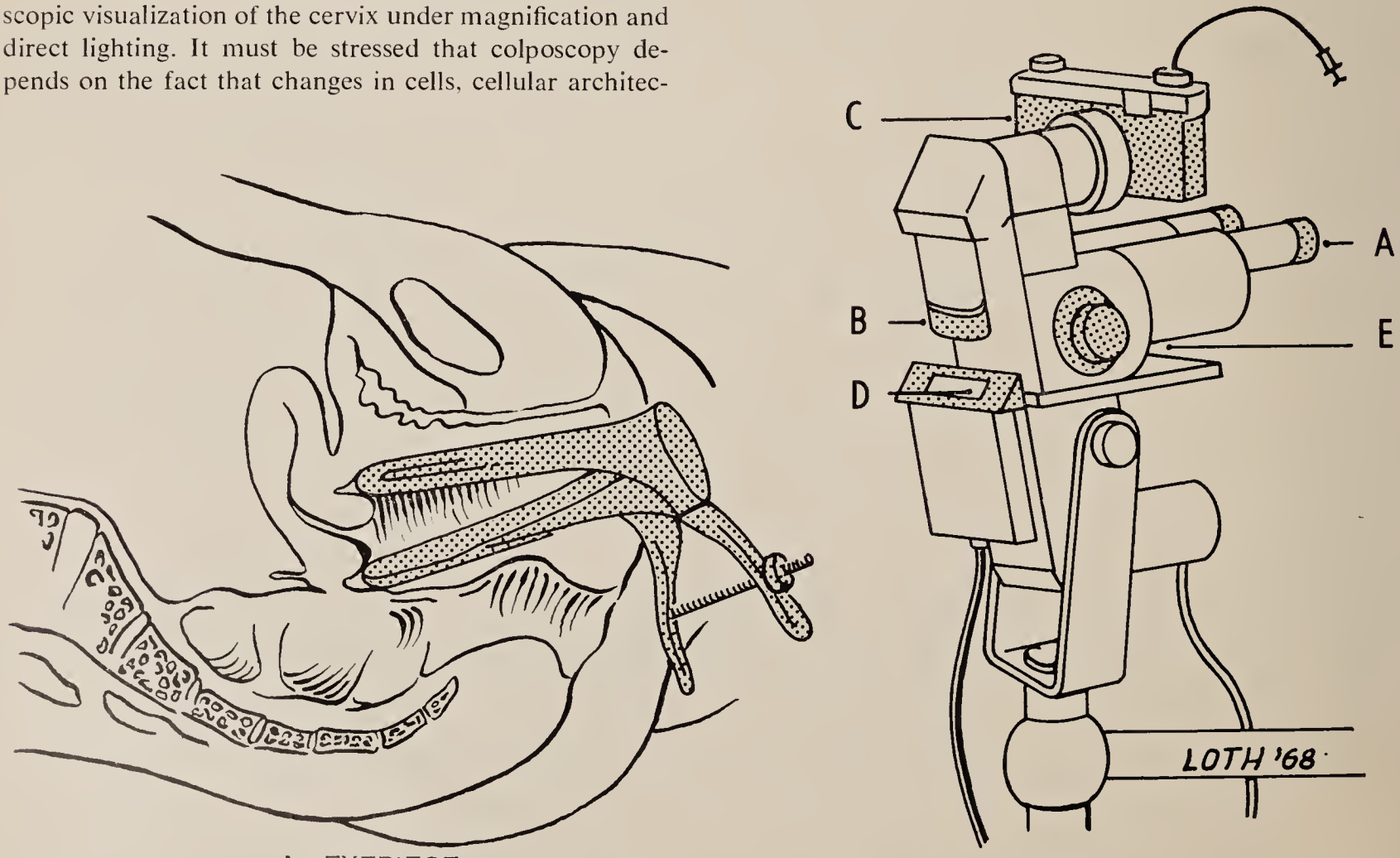
The colposcope was introduced in Germany in 1925 by Hans Hinselmann as a diagnostic instrument for carcinoma of the cervix. Unfortunately the late German gynecologist developed a classification of lesions of the cervix which was both confusing and arbitrary and subsequently hampered progress. In 1928 Schiller introduced Schiller's iodine test and this was welcomed by Hinselmann, who incorporated its use into his technique calling it "extended colposcopy". It was not until 1945 that Papanicolou and Traut introduced cytology of cervical smears; however this technique at present has a much wider use in screening for carcinoma of the cervix than does colposcopy. Colposcopy is widely used in Germany, Austria, Switzerland and France, slightly in South America, with increasing numbers of reports coming at last from North America.

## THE PRINCIPLE AND TECHNIQUE OF COLPOSCOPY

The principle is simple. It consists of direct stereoscopic visualization of the cervix under magnification and direct lighting. It must be stressed that colposcopy depends on the fact that changes in cells, cellular architecture and surface epithelium vascularization are detectable with surface enlargement.

The colposcope itself is a binocular instrument (figure 1) mounted on an adjustable pole stand with a transformer at its base. Most current models are compact and mobile. The magnification routinely used is x 10, however most instruments also carry x 6, x 16, and x 25 lenses, all interchangeable without refocusing. At this point we must distinguish the *colposcope* from the *colpomicroscope* which was developed after the colposcope by Antoine and Gurnberg. The colpomicroscope visualizes cervical *histology* at microscopic magnification, and must be approximated to the cervical tissue to be examined. It remains primarily a research tool.

The average focal length of the colposcope is 20 cm. and therefore the instrument *does not* enter the vagina (figure 1). Examination by an experienced gynecologist takes 2 - 4 minutes. The method is simple and can be performed without discomfort to the patient. The patient is prepared in the lithotomy position and a bivalved self-




A - EYEPIECE
B - GREENFILTER - SWINGS DOWN INTO PLACE
C - CAMERA FOR COLPO PHOTOGRAPHY
D - LENSE
E - FOCUS, FOCAL LENGTH = 20 CM (FROM D TO CERVIX)

FIG. 1. Zeiss Colposcope, with photographic attachments, in position.

retaining speculum inserted. The colposcope is then moved into position and colposcopic examination performed.

Routine colposcopic examination:

1) observe cervix with naked eye and take pap smear for cytology if not previously done;

2) some gynecologists then view the cervix through the colposcope without wiping the cervix;

3) 3% aqueous acetic acid solution is applied with a large cotton applicator to remove mucous and cause slight tissue swelling to increase clarity and accentuate any abnormal cervical architecture;

4) install green filter on colposcope and observe vascular patterns and check the intercapillary distances;

5) apply Schiller's iodine solution and inspect for any areas which have not taken up the dye (diseased cells have decreased glycogen content and therefore do not take up the dye and remain pale, whereas normal tissues darken);

6) if *colpophotography* is going to be employed then solutions such as acetic acid, Schiller's, and other irritating substances must be avoided as they interfere with translucency of the surface epithelium. For photography physiological saline is the best.

## FEATURES AND TERMINOLOGY OF COLPOSCOPY

The gynecologist learning colposcopy must rethink his clinical definitions concerning cervical lesions and possibly then his diagnosis and treatment of such lesions may become more exact. In contradistinction to a histological study, colposcopy reveals no *one* change or a group of changes specific for malignancy, but marked qualitative features indicative of a neoplasm. Early carcinoma of the cervix is discovered by colposcopy, not because a miniature carcinoma, exaggerated by magnification is seen, but rather because early carcinoma induces abnormalities in the epithelium which are more easily seen.

According to Per Kolstad[5], of the Norwegian Radium Hospital, a colposcopic classification is most easily determined on the basis of the following:

1) *Vascular patterns* — more easily seen with a green filter in place (introduced by Kraut in 1939) — abnormal patterns on the epithelial surface may be compared to: (i) commas, (ii) corkscrews; (iii) spaghetti forms; (iv) vascular hypertrophy.

2) *Intercapillary distance* — this distance increases as oxygen tension deceases in carcinoma of the cervix.

3) *Colour tone* relative to normal mucosa judged with the green filter in place — a typical epithelium of carcinoma in situ is usually darker than dysplasia or normal tissue; invasive carcinoma tends to be *white* due to heaping up of the epithelium.

4) *Surface patterns* — normal tissue is usually *smooth;* ectopic columnar cells at the transformation zone is often *papillomatous* or *grape-like;* in *coarse, uneven,* or *nodular* areas invasive carcinoma must be suspected.

5) *Borderline* of area of lesion against adjacent normal tissue — division between normal tissue and carcinoma in situ is usually *sharp;* division between normal tissue and dysplastic areas is usually *diffuse*; transformation zone of squamous and columnar epithelium may vary and still be normal.

Using these 5 criteria Kolstad divides cervical lesions into 7 categories:

(i) normal cervix

(ii) benign lesions — inflamation, ectopy, transformation zone, cervical polyps.

(iii) leukoplakia without evidence of malignancy

(iv) dysplasia—regular or mosaic vessels; slightly increased intercapillary distance; smooth surface; normal colour or slightly darker; diffuse border.

(v) carcinoma in situ — coarse irregular vascular pattern; definite increase in intercapillary distance; granulated surface; darkened tone; sharp border.

(vi) early invasive carcinoma
(vii) invasive carcinoma

} very important here are the abnormal vascular patterns.

According to Hans Limburg[8] abnormal colposcopic lesions may be divided into 5 categories as follows: (brackets indicate his statistical evaluation of chance of the lesion being carcinoma in situ):

1. Simple leukoplakia (9.4%) — whitish plaque which may or may not be visible to the naked eye.

2. Ground leukoplakia (13.2%) — yellowish white area with red blood vessel stippling.

3. Mosaic leukoplakia (9.9%) — yellowish white with a mosaic pattern (figure 3).

4. Atypical blood vessels (9.9%) — corkscrews or commas.

5. Erosio vera (9.8%) — loss of surface epithelium.

Factors involved in leukoplakia are decreased transparency of epithelium from thickening in number of cell layers or from increased keratinization or both.

The use of the colposcope involves a study of the various classifications (there are many others) and practice in recognizing these lesions. Colpophotographs may be helpful here, before actual clinical inspections.

## COMPARISON OF COLPOSCOPY AND CYTOLOGY IN THE SCREENING FOR CERVICAL CARCINOMA

It must be stressed that the two disciplines of colposcopy and exfoliative cytology are NOT choices in the field of cervical cancer detection, but should be used to complement each other. Since these two techniques involve entirely different principles the results of their parallel application should decrease the possibility of error when used simultaneously. The advantages and limitations of each will be briefly outlined, followed by relevant statistical evidence of complementary uses.

*In Review of Cytology*

The results lie in the smear; however little training is required of the clinician before he can take a good smear. The slide is then sent away to a trained cytopathologist, who can serve *dozens* of clinicians with interpretations of their patients' smears. In this way the clinician is handed a diagnosis quickly and easily.

Cytology also has the added advantages of giving an hormonal assessment of the cervix, identifying infections, and the microbiology of the cervix. Most important is the ability of the smear to detect *endocervical* (and endometrial) lesions which may lie beyond the range of the colposcope.

Errors lie in poor preservation, transport and staining of the slide by untrained assistants. A significant number of *false negative* smears have been reported in cases of malignant leukoplakia, where the keratin on the cervix is thick enough to prevent exfoliation of cancer cells, leading to a false negative report.

*Summary of cytology:* easy technique; less time consuming; requires less individual training as one cytopathologist can serve many clinicians; good possibility of picking up endocervical lesions; possibility of false negatives in leukoplakic lesions.

*Uses of the Colposcope*

According to Per Kolstad (6b):

1. Diagnosis of cervical lesions, especially after suspicious repeat smears.

2. To increase detection of malignancies of cervix by picking up cases in which smear has been a false negative especially in cases of leukoplakia.

3. Very important for pinpointing biopsy sites on the cervix and thereby cutting down on unnecessary cervical biopsies and cervical cones.

4. Helps determine the type of therapy which will be the best, by more exact evaluation of the type and extent of the lesion.

5. Colposcopy is also of value in the study and follow up of questionably pre-cancerous lesions of the cervix, as very good records may be kept on colpophotographs.

## LIMITATIONS OF COLPOSCOPY

1. Most of the original work was written in German, however in the last few years with wider use of the colposcope this is no longer a drawback as many excellent reports have now been published in English.

2. Here in North America the necessity of extra training and foreign travel may in some instances be a drawback. Study and practice are very important in colposcopy and if taught in a resident program might prove less a barrier.

3. The cost of a colposcope is not a truly prohibitive factor for a clinic, but possibly for a single clinician.

4. Many clinicians have said the main limitation of colposcopy lies in the fact that the endocervical canal is not visible and that it has been thought that most cervical carcinomas arise in the canal. However the self-retaining speculum itself will open the cervical external os to some degree and the use of a cervical canal speculum will facilitate visualizing the canal to a large extent. This procedure is easy and painless in the multiparous patient. These facts seem to refute the original argument, as does the work of Franque, who, as early as 1930, asserted that endocervical carcinoma nearly always starts near the external os, eg. at the junction area of squamous and columnar cells, and therefore will normally be seen. In 1952 Held and in 1956 Limburg[8] both stated that only 3% of pure endocervical carcinomas existed; thus this does not seem much of a drawback. Other advantages of colposcopy are better illustrated in the following figures, which help show the increase in number of cases of carcinoma in situ discovered when colposcopy is constantly used.

Navratil, Bajardi, and Nash[9] list the advantages of the use of colposcopy *PLUS* cytology as the following:

1) Simultaneous use results in no loss of time as it takes 3 - 4 minutes by the practiced clinician and simply replaces the normal speculum examination without any discomfort to the patient.

2) Colposcopic diagnosis is immediate and arrives at its results merely through examination of the patient.

3) Accuracy of biopsy site with decreased number of biopsies and cones is also to be stressed.

4) With negative cytology, colposcopy can dispose of suspicion on the basis of clinical examination.

5) Colposcopy also enables one to perform target pap smears for cytology.

## SUMMARY OF COMPARISON

Neither method is perfect — and both have valid limitations but *together* they are approximately 99% accu-rate. There is no infallible method of screening for lesions of the cervix. However because cytology and colposcopy employ different principles their results must complement each other and yield results which are additively better. Each study quoted below confirmed the diagnosis apparent from cytology or colposcopy or both by biopsy.

## STATISTICAL ACCURACY OF COLPOSCOPY AND CYTOLOGY

| *Investigator* | *Cytology* | *Colposcopy* | *Combined Accuracy* |
|---|---|---|---|
| Navratil (9) | | | |
| 1952 | 87% | 79.1% | 98.8% |
| 1962 | 85.5% | 91% | 98.7% |
| R. Rambout (13) | 93% | 91% | 98% |
| Kolstad (6b) | 88.6% | 85% | 97.2% |
| Limberg (8) | | | 99.4% |

"For overall discovery of cervical lesions most figures available show that cytology and colposcopy yield comparable results in mass screening and improve the total detection rate."

### Statistics Concerning False Negative Smears (Including Those Associated With Carcinoma In Situ).

Freidell, Hertig and Younge report 30.6% false negatives in 121 cases.

Koss reports 30 - 40% false negatives; Navratil, Nyberg and Coppleson report 10 - 35% false negatives.

Other reports:

Graham reports cytology to be 96% accurate with invasive carcinoma and 89% accurate with carcinoma in situ. Similarly Messelt reports 97.7% and 88.0% respectively. There has been a significant increase in the incidence of carcinoma in situ as calculated by Limberg (in Hamburg) from 4.2% to 27.7% of ALL cervical carcinomas. Limburg estimates the error in carcinoma in situ with the smear as 11.1% and by colposcopy as 3%.

All these reports serve to bear out the fact that colopscopy and cytology are complementary and have served to increase the overall discovery rate of *early* cervical carcinoma, especially at the carcinoma in situ stage, thereby increasing the prognosis for a substantial group of females with cervical carcinoma.

## SUMMARY

1. A description of colposcopy has been outlined including: history; equipment, principle and technique; the lesions and a study of the evaluation of lesions.

2. A comparison has been presented of cytological and colposcopic techniques in cervical carcinoma screening outlining the positive and negative features of both.

3. Relevant figures representing the accuracy of both methods and their complementary nature have been presented.

4. Now the question of use of colposcopy in general screening programs must be asked. In Europe this is the practice commonly and the reasons for such seem strong, yet here in North America very few clinicians have diverged from the single method of cytology. Application of both methods will lead to optimum results. Colposcopy represents in my opinion a valuable addition to the clinical diagnosis of cervical lesions, decreasing the need of repeat pap smears, and leading to early tissue diagnosis. Again it should be noted that biopsies are only taken in areas of colposcopically abnormal architecture thereby decreasing total biopsy numbers and cervical cones.

5. In questioning the *practical value* of the colposcope this statement seems to tie the article together.

> "A physician who omits an examination (by colposcope) is much the same as an astronomer who insist that he can see stars without a telescope. Although such a theory may be true, it is only a fraction of the truth."[17]

*ACKNOWLEDGEMENTS*

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## *Clinicopathological Conference*

# *Amenorrhea And Infertility In A 27 Year Old Housewife*

### CLINICAL HISTORY

#### First Admission — 1962

Mrs. E. W., a 27-year-old housewife of Austrian origin para 1, gravida 1, was admitted to the T.W.H. for investigation of functional amenorrhea. Since menarche at age thirteen she had complained of irregular periods. When menstruation occurred, flow lasted eight to ten days, was menorrhagic and many clots were passed. There was no associated dysmenorrhea. In 1956 she had delivered a 7 lb. 8 oz. female child uneventfully. Since the birth of her first child she had menstruated only twice each year and now was infertile for three years duration.

At this time functional enquiry noted that since coming to Canada she had been suffering from heat intolerance and her voice was deepening. She also noted that hair was increasing on her breasts, arms, legs and chin, and that she had gained weight. As a child she had scarlet fever. There was no past history of tuberculosis, diabetes mellitus or rheumatic fever. She had not undergone any surgery and had no known thyroid disease.

Physical examination revealed an obese female with mild hirsutism on face, breasts and legs. Head and neck revealed no abnormalities. The chest was clear to inspection, palpation, percussion and auscultation. The heart rate was 80 per minute, blood pressure was 120/80, and heart sounds were normal in all areas. No murmurs were detected. Abdominal examination revealed an obese abdomen which was non-tender. No masses were felt. Neurological examination was essentially normal.

Laboratory investigation yielded the following results: Urine specific gravity was 1.024, pH was 7.5, and the sample was negative to albumin, sugar and ketones. Microscopic examination yielded an occasional RBC and 2 - 4 WBC per HPF. 24-hour urine excretion was 1070 cc in volume. Creatinine was 1.51 gm / vol. and 17-ketosteroids were 5.7 mg. / vol. BMR was 100%.

Examination under anaesthesia revealed good pelvic support. The uterus was anteverted, mobile and of normal size. The left adnexa were clear. The right ovary was mobile and enlarged to approximately 5cm. x 4cm. and appeared somewhat cystic. Curettage at this time yielded a proliferative phase endometrium.

#### Admission — Jan. 1964

The patient was followed and readmitted in January 1964. She complained at this time of further increase in facial and body hair. Her voice had become deeper and her breasts had regressed in size. Weight gain over the past eight years was sixty lbs. and could not be explained solely on a dietary basis. She now desired a second pregnancy.

E.U.A. at this time showed no significant changes. Dilatation and curettage were performed and at laparo-

tomy the ovaries were shown to be approximately 2½ cm. in diameter. The outer surface was shiny and the ovaries were quite hard. Bilateral wedge resections were performed and a normal appendix was removed.

The patient was carefully followed with repeated D. & C.s and in 1967 delivered a healthy male infant weighing 6 lbs. 12½ oz. at term. Her course has been uneventful to date.

### Differential Diagnosis

The problem of amenorrhea and infertility requires consideration of the entire reproductive system, from hypothalamus to uterus. In this patient many congenital anatomical and biochemical abnormalities may be ruled out as she was able to give birth to a healthy infant. This required ovulation, fertilization and a suitable endometrium for implantation of the ovum. Virilism is a demonstrable sign in many endocrinological disorders. For definitive diagnosis a complete endocrinological profile is essential in studying these patients. Urinary 17-ketosteroids will be elevated in adrenogenital syndrome and adrenal hyperfunction due to hyperplasia or tumour, but will be normal in the polycystic-ovary syndrome. A 17-ketosteroid level of 5.7 mg / vol. certainly lies within normal limits.

Pregnanetriol excretion is elevated in adrenocortical tumour but normal in adrenogenital syndrome and Stein-Leventhal syndrome. With a trial of cortisone, the 17-ketosteroid excretion will be depressed if the findings are caused by adrenal tumour (non-autonomous). Cushing's disease, Cushing's syndrome or a functioning basophilic adenoma of the pituitary must be ruled out. X-rays of the sella turcica are helpful. Thyroid disease may be ruled out by normal BMR, PBI, T4 uptake and $I^{131}$ studies. To definitely rule out hilar cell tumours, adrenal rest tumours and arrhenoblatomas the ovaries must be visualized either through culdoscopy, laparoscopy or at laparotomy.

In our patient, the findings of amenorrhea, virilism, infertility and an enlarged ovary in the presence of normal 17-ketosteroids strongly suggests Stein-Leventhal syndrome. Definitive diagnosis can only be made at laparotomy by the pathologist.

## PATHOLOGY

### Admission — Jan. 1964

The curettings on gross examination were composed of several pieces of greyish white, friable tissue. There were some interspersed blood clots. Microscopic examination revealed portions of endometrial glands and stroma in the proliferative phase. Several fragments exhibited markedly a typical hyperplasia which in areas had the appearance of adenocarcinoma. In these areas large irregular glands with intraluminal tufting replaced the stroma; cuts showed stratification and a moderately pleomorphic and vacuolated appearance. Those areas were regarded as carcinoma in-situ of the adenomatous type. On gross examination the wedge of right ovary had an outer surface which appeared cystic. The remaining cut portion revealed several cystic areas near the cortex. The section of left ovary had an outer surface which was slightly nodular and the cut surface showed cystic areas which were lined with a smooth, glistening membrane. Microscopic examination disclosed an outer cortical layer which was less cellular and more fibrotic than the underlying ovarian stroma. In the medulla were large follicular cysts which exhabited a well defined theca interna. A few follicles contained a myxomatous cellular stroma. No corpora lutea or corpora albicantia were seen.



FIG. 1. Low Power micrograph of the wedge section of left ovary showing multiple cortical cysts.

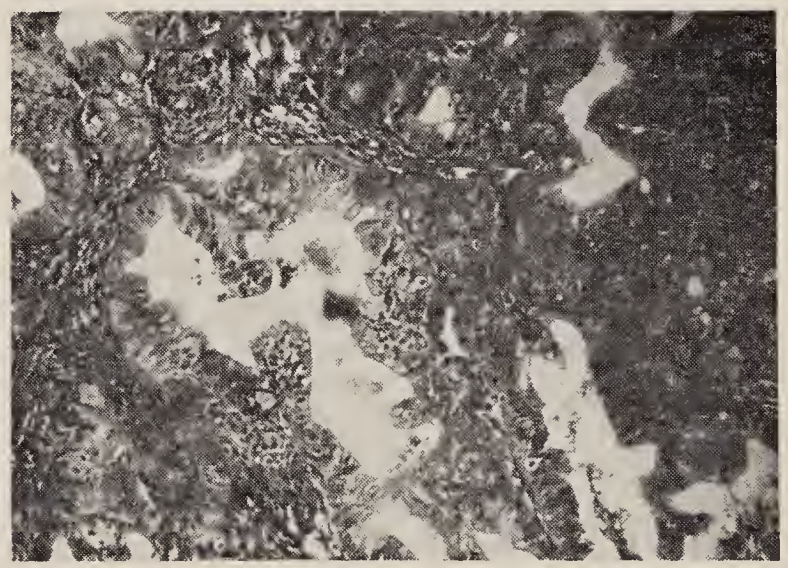


FIG. 2. High power micrograph showing carcinoma in-situ of the endometrium.

## PATHOLOGICAL DIAGNOSIS

Adenocarcinoma in-situ of endometrium.

Portion of the right and left ovaries showing multiple follicular cyts and cortical stromal fibrosis compatible with Stein-Leventhal syndrome.

## STEIN-LEVENTHAL SYNDROME — DISCUSSION

Infertility, oligomenorrhea or amenorrhea and enlarged polycystic ovaries comprise the Stein-Leventhal syndrome as described by the authors in 1935. Frequently

associated but not pathognomonic signs are hirsutism obesity and clitoral hypertrophy. Women presenting with gross adrenal hyperfunction may present with similar symptoms and signs including polycystic ovaries although the latter finding is rare (Perloff, 1958). In the ensuing discussion we will try to present this syndrome as an exercise in preliminary examination, special investigation and modern methods of treatment.

The diagnosis should be suspected in young women presenting with oligo- or amenorrhea before they reach the stage of infertility complaints. Usually the history is one of episodic amenorrhea lasting from several months to more than a year. Some patients present as primary amenorrhea.

In the physical examination note should be taken of excessive facial, chest and leg hair. On pelvic examination clitoral changes may be present. Enlarged cystic masses may be felt in one or both adnexa. If bimanual examination is inconclusive, E.U.A. is warranted. Many clinicians feel there is a definite place for culdoscopy and peritoneoscopy. Curettage should always be performed. Usually the endometrium shows either proliferative or secretory changes. Cystic glandular hyperplasia has been found to be present in up to thirty percent of cases (Roberts, 1960). Carcinoma in-situ of the endometrium has been described in conjunction with the Stein-Leventhal syndrome (Cirns, 1967).

Special investigation leads to the field of hormone assay. Urinary 17-ketosteroids may be elevated or normal; urinary pregnanetriol and pregnanediol are within normal limits. Urinary oestrogen levels are usually similar to those found in the follicular phase of the normal cycle (Mahesh and Greenblatt, 1964). Increased levels may be found in association with endometrial hyperplasia. The plasma testosterone level is usually elevated. This, however, is not diagnostic.

Shearman has described two investigations which are of specific value in this syndrome. These are: (1) urinary levels of delta$^5$-pregnenetriol and pregnanetriolone and (2) the effect of diagnostic gonadotrophin stimulation on ovarian size and urinary estrogens. Many workers have found increased levels of delta$^5$-pregnenetriol in preoperative studies on patients with the Stein-Leventhal syndrome (Stern and Barwell, 1963, Shearman and Cox, 1961). Others, however, found normal values, or increased values only after stimulation. The detection of pregnanetriolone in urine has been of value. Normally this steroid is absent from urine; detection occurs in patients with adrenal hyperplasia associated with adrenogenital syndrome or Cushing's disease and in patients with Stein-Leventhal Syndrome. A detectable urinary pregnanetriolone combined with a normal urinary 17-ketosteroid is almost diagnostic. Unfortunately assay methods have as yet not been perfected.

It has been shown that women with polycystic disease of the ovaries develop gross ovarian enlargement and a marked increase in excretion of urinary estrogens after homologous or heterologous FSH stimulation. This does not occur in patients with other forms of amenorrhea. Best results are obtained using human menopausal gonadotrophin or pregnant mare serum gonadotrophin (Shearman and Cox, 1966).

Treatment of Stein-Leventhal syndrome consists of primarily inducing ovulation. Hirsutism cannot be treated — it can, however, be arrested. As noted above, patients with Stein-Leventhal syndrome show markedly exaggerated response to FSH stimulation. Therefore it is advisable to use one of three methods of treatment: (1) Wedge resection of ovaries (2) Clomiphene therapy or (3) adrenocortical suppression. Surgery, if initially successful, effects a permanent cure of anovulation in most cases even though no definite reason has been demonstrated why this should be so. Clomiphene is equally effective, but only as long as treatment is continued. Adrenocortical suppression should be reserved for those patients in whom wedge resection is unsuccessful.

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# *Eponyms And The Men*

FRANCOIS MAURICEAU (1637 - 1709), the leading French obstetrician of his time, originated the *Mauriceau maneuvre* used in breech extraction. Little is known of his early training, but his extensive practice of midwifery, both private and in the Hôtel Dieu of Paris (then the greatest establishment in Europe for lying-in women), fully qualified him to lay down rules of procedure formulated as a result of his wide experience. His epochal 1668 treatise corrected many of the erroneous teachings of former times and gave directions as to the conduct of normal labour, version, and the management of placenta praevia. André Levret said that Mauriceau "drew from the cradle" the art of midwifery. In his later 1694 work, Mauriceau related that in August of 1670 he supervised a particularly difficult labour in a 38-year-old primipara with a deformed pelvis. Hugh Chamberlen the Elder, renowned physician to Queen Catherine, wife of Charles II, had arrived in Paris several months earlier and let it be known that he possessed a secret means of facilitating deliveries hitherto impossible. On this occasion Mauriceau expressed the opinion that the patient could not be delivered; upon consultation, Chamberlen affirmed that he could do so safely within a quarter of an hour. After three hours he desisted and one day later the woman died undelivered. Mauriceau stated that the ensuing autopsy disclosed a uterus torn and perforated in many places by Chamberlen's early and crude obstetrical forceps. In all fairness, however, it must be added that Chamberlen later translated Mauriceau's 1668 text into English and in so doing made a substantial contribution to the progress of midwifery in England. Excerpts from this translation make for an extremely fascinating study of seventeenth-century medical writing, as shown by the following description of manual vaginal examination in pregnancy:

> "The Midwife must from time to time taste (touch) the inward Orifice with her Finger, to know whether the Waters are ready to break, and whether the Birth will soon after follow: she must likewise anoint all the bearing place with emolient Oils, Hogs-grease, or fresh Butter, if she perceive that they can hardly be dilated, and all the while she must be near her Woman, to observe her Gestures diligently, her complaints and pains; for by this they guess pretty well, how the Labour advanceth, without being obliged to taste (touch) what comes from her Body so often."

JOSEPH BOLIVAR DELEE (1869 - 1942), American, is known for his instruments and inventions, especially the *DeLee-Hillis foetal stethoscope,* the suction aspirator, bladder retractor, and some forty others. In addition, one of the outstanding textbooks of obstetrics in modern times was written by DeLee in Chicago. Beginning in Vienna in 1907, he outlined the work in a single burst of energy in twenty-four hours, but he required the next four years to actually write the tome. Each page was revised many times and nearly one thousand illustrations were drawn from photographs or sketches at the bedside. When published in 1913, it was considered the most meticulously prepared and definitive book in its field. DeLee is also remembered for the description of a method of low cervical cesarean section, for his establishment of the Chicago Lying-In Dispensary, and for his particular concern with improving prenatal care among the indigent in Chicago.

A recent contribution to the evolution of obstetrical forceps was made by Dr. JOHN MANN (1901 - 1960) of this university. Born in Coatbridge, Scotland, Mann came to Canada at the age of ten to reside in Sault Ste. Marie. He spent an adolescent apprenticeship at the Algoma Steel Company; his engineering skills later proved their worth following his graduation in medicine from Queen's University in 1927. Having completed training in obstetrics and gynecology at the Toronto General Hospital, Mann was appointed to the staff in 1930 and eventually achieved an associate professorship here. He is described as a man of "great ability to analyze a problem, to suggest modifications in method and apparatus and to utilize his mechanical ingenuity to design efficient instruments of maximum simplicity." In 1956 he received an award from the Royal College of Obstetricians and Gynecologists for the best essay concerning the construction and use of obstetrical forceps. Following an extensive study of earlier instruments, Mann designed an improved model which was tried at T.G.H. for three years and outlined in a 1957 paper; it now bears his name. The modification involved a special lock split in two, allowing each blade to slide back and forth along uncrossed shanks. The instrument could thus be fitted to a head in asynclitism and also could not be compressed, thus avoiding corresponding compression of the foetal head. Doctor Mann, an enduring friend of the student, was not only an influential teacher and speaker in obstetrics but was also an intelligent and compassionate physician.

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**Student Research**

# *The Effect Of Methylprednisolone and ACTH on Lactate Turnover*

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*G. Hetenyi Jr., M.D., Ph.D.*

## INTRODUCTION

It is known that adrenocortical steroids accelerate hepatic gluconeogenesis and increase the rate of production of glucose in dogs (1). However, neither the percursors nor the fate of this excess glucose is known. Since these hormones cause a large increase in plasma lactate level, it was thought that perhaps increased glucose production was a result of an increase in recycling of lactate via the Cori cycle. We set out to investigate this possibility by measuring the turnover rate, essentially the rate of production of lactate in dogs, using the tracer infusion method of Forbath et al (2) with L(+)-lactate-U-$^{14}$C as the tracer. The effects of methylprednisolone and ACTH on lactate turnover and on the reincorporation of lactate-$^{14}$C into glucose were studied.

## METHODS

The experiments were carried out on normal dogs in the postabsorptive state, weighing 8-12 kg, trained to stand quietly in a Pavlov stand. Periodically, during the 240 min. course of the experiment, the blood samples taken were centrifuged and after deproteinization the lactic acid and glucose were separated on a Dowex-1 resin column. Lactic acid, together with other organic acids, were eluted from the column with $Na_2SO_4$. Lactic acid was isolated from the eluate and its specific activity determined, according to Brin and Olson (3). The specific activity of glucose was calculated according to Jones (4). The specific activity of the sixth carbon atom of glucose was calculated in all experiments according to Reichard (5). Using thse data the amount of $^{14}$C incorporated into glucose and hence the extent of recycling could be determined. Plasma glucose and lactate levels were measured enzymatically.

## RESULTS

Each dog served as his own control. Five of the dogs were injected with methylprednisolone (Depo-Medrol) - 4 mg/kg/day for seven days; four dogs were injected with ACTH (Duracton) — 40 units/day for 4 days to 6 days — and the amount of $^{14}$C incorporation was compared with the control value. All injections were intramuscular.

It was found that methylprednisolone caused an increase of 6 - 10 fold in the plasma lactate level in all five dogs. The rate of appearance of lactate was increased 3-fold on the average. The increase in the rate of lactate production after ACTH is smaller, approximately 1.7 fold (the response was less uniform: one dog did not respond at all). The plasma lactate level after ACTH treatment increased only slightly.

## INCORPORATION OF CARBON ATOMS INTO GLUCOSE

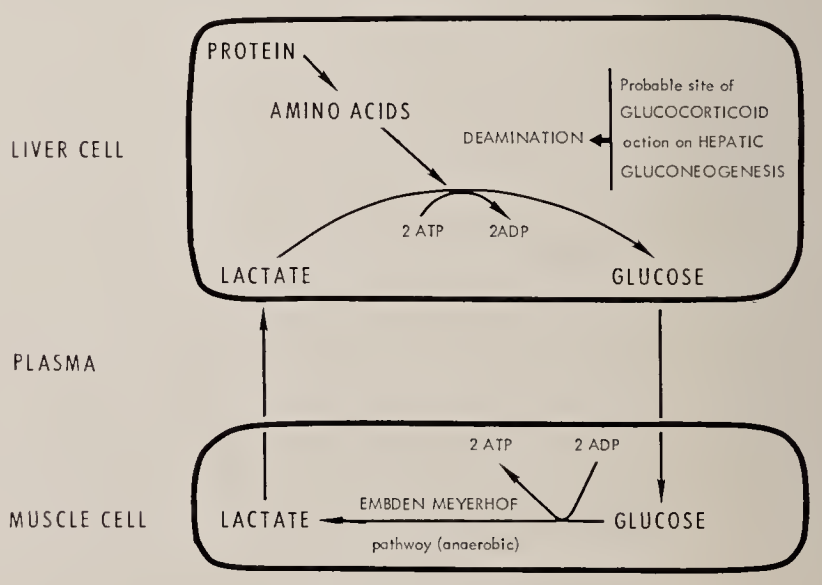
The incorporation of $^{14}$C into the 6th carbon atom of glucose was very low in all cases, much less than 1% of the total carbon atoms removed from the circulation as lactate between the 30th and 240th minutes of the experiment. Further, it was found that the incorporation did not increase significantly after either ACTH or methylprednisolone.

The ratio of glucose specific activity to that of glucose C-6 specific activity was approximately 1:5, indicating a preferential distribution of $^{14}$C as predicted (5). Neither ACTH nor methylprednisolone changes this distribution significantly.

## DISCUSSION AND CONCLUSIONS

The results indicate that methylprednisolone and ACTH increase plasma lactate turnover. But this increase in turnover does not lead to an increased *preferential* recycling via the Cori cycle into glucose. The excess glucose must come from some other source, probably protein.

PATHWAYS IN THE CORI CYCLE




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# **Recent Advances** *The Demise Of Erythroblastosis Fetalis*

## INTRODUCTION

Erythroblastosis fetalis, as a disease entity affecting the newborn infant, has been known to medical circles for thousands of years, and yet, not until 1939 was progress made in ascribing an etiology to this disease.

At that time, Dr. Philip Levine investigated a case of an intragroup transfusion reaction in which a Group O mother was transferred post partum with blood from her Group O husband.[1] She had previously been delivered of a stillborn infant and had sustained a serious post partum hemorrhage. Following transfusion, the woman developed a severe transfusion reaction. Dr. Levine proposed that the woman had become sensitized during her pregnancy to an unknown antigen on the babies red blood cells. This antigen which was present on the father's cells was absent from the mother's. Further investigation of this and similar cases during the next few years led to the discovery of the Rhesus (Rh) blood group system and elucidation of the pathogenesis of Rh erythroblastosis fetalis: that fetal Rhesus (Rh) positive red blood cells in the circulation of the Rh negative mother after delivery in the puerperium or during pregnancy after previous incompatible pregnancies or transfusions cause immunologically competent maternal cells to produce a specific antibody to the Rh antigen. Subsequent pregnancy with an Rh positive fetus causes an anamnestic response of maternal antibody titre, with complete or saline activity 19 S gamma globulin appearing first as the primary response, followed by a secondary response of incomplete or albumin active 7 S gamma globulin. This 7 S gamma globulin enters the fetus transplacentally to produce lysis of fetal red blood cells and fetal morbidity and/or mortality due to stillbirth, anemia, and kernicterus.

Recent advances in obstetrics, neonatology and hematology such as preterm induction of labor, amniocentesis with studies of amniotic fluid bilirubin, intrauterine transfusion, and post natal exchange transfusion have greatly reduced the consequences of this disease. However, the perinatal morbidity and mortality due to Rh erythroblastosis fetalis is still so high as to be a significant public health problem.[2]

### Immunological Background

About forty years ago it was shown during studies on diphtheria and tetanus toxoid immunization that, under proper conditions, passively administered antibody could block immunization.[3] In recent years it has been noted that when an ABO incompatibility between mother and baby exists in addition to an Rh isoimmunization, the hemolytic effects on the baby are often significantly less severe than if the Rh incompatibility alone had been present.[4] Two theories have been proposed to explain this phenomenon:[2]

1. The cells hemolysed by anti-A and/or anti-B are taken to the liver where there is little or no immunologically competent tissue.
2. The immunologically competent cells of the spleen are already too "busy" making more anti-A and/or anti-B and hence no anti-Rh is made.

Regardless of which theory (if either) is correct, the fact remains that passive immunization will prevent active immunization under the proper conditions.

Because of this fact, several experiments to prevent Rh isoimmunization were first undertaken in male Rh negative volunteers. They were injected with ABO compatible Rh positive blood and subsequently some were treated with pure anti-Rh gamma globulin and some were not. None of the treated group became immunized to the Rh factor while many members of the control group did.

Encouraging results like these led to clinical trials in Rh negative pregnant women delivered of ABO compatible Rh positive babies. The failure rate has been less than 0.5 per cent and these failures have been explained on several bases:[6]

1. Some women may have become isoimmunized prior to or during their first pregnancy and although the material has been given within 72 hours post partum, active antibody has already been produced.
2. The passive antibody has been administered after 72 hours post partum.

### The Active Agent

The material used in these trials and now commercially available* is the Cohn Fraction II of the plasma proteins, containing almost pure 7 S gamma globulin. This has been obtained by a cold alcohol method of fractionation from pooled donor plasma containing high tires of anti-Rh.[2] Plasma is not used directly because of the risk of transmission of serum hepatitis and because experiments have shown that the suppression of active antibody synthesis may be dose related to the amount of passive antibody used. Some experiments in animals have demonstrated that improper dosages may fail to protect the recipient and may even enhance active antibody synthesis.[7]

Until now, the source of this plasma has been actively isoimmunized Rh negative women. With gradual elimina-

*RhoGAM, Ortho Research Foundation. Raritan, New Jersey, U.S.A.

tion of the disease erythroblastosis fetalis, the future source of the anti-Rh plasma will have to be actively immunized Rh negative male volunteers.

### Time of Injection

The passive antibody must be injected intramuscularly into the recipient within 72 hours of the termination of her first sensitizing pregnancy if adequate protection is to be obtained.

It has been shown by the differential staining technique of Kleihauer and Betke that fetal red blood cells may appear in the maternal circulation as early as the second trimester[2] and yet the consequences of maternal antibodies affecting fetal red blood cells do not usually become manifest until the second pregnancy with an Rh positive fetus. The lack of antibody production during the first pregnancy of an Rh negative mother with an Rh positive fetus is perhaps due to the high levels of circulating maternal steroid hormones during pregnancy or the fact that a major transplacental bleed at parturition is required before sensitization and subsequent active antibody synthesis can begin.[6]

## CONCLUSION

Thus, a disease elucidated less than thirty years ago may be virtually eliminated within one generation of childbearing in areas where modern concepts of obstetrics are practiced. For millions of already sensitized women, this landmark in medical progress has arrived too late. Erythroblastosis fetalis in outlying areas and due to other blood group systems than the Rh system will continue to be seen.[2]. However, a major cause of perinatal morbidity and mortality is on the wane.

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# *On Using Statistics - A Discussion Of The Dangers Of Therapeutic Abortion*

INTRODUCTION

The overall mortality from therapeutic abortion performed in a modern hospital setting is still higher than the present maternal mortality rate. Statistics published in Denmark[1 2 3] indicate the mortality rate for therapeutic abortions to be 0.7 per thousand, whereas maternal mortality in the United States in 1963 was 0.36 per thousand live births[1], and in Canada in 1965 was 0.32 per thousand live births[4]. That is, maternal mortality is one-third to half as great as that due to therapeutic abortions. In addition, it is noted in the Danish series that non-fatal serious complications occur in approximately 3% of cases, and, depending on the procedure employed (dilatation and evacuation, hysterotomy, etc.) and the period of gestation, morbidity rates may go as high as 15%.[1 2 3]

Such statistics have been used to strike fear into the hearts of obstetricians and lawmakers alike, in support of the hypothesis that therapeutic abortion is medically a grave undertaking. The Council of the Royal College of Obstetricians and Gynecologists in Britain used such statistics to help establish its policy on therapeutic abortions[2], and Eastman and Hellman make use of them in their textbook.[1] The statistics themselves are undoubtedly reliable, but it is not clear exactly how one can conclude from them that therapeutic abortion is, in fact, a "grave undertaking."

There are at least two major weaknesses in the use of the present statistical information: first, the failure to acknowledge the morbidity of pregnancy in general; and second, the failure to acknowledge the nature of the population upon whom abortions are performed and in whom the fatalities and complications occurred. These two areas will be discussed separately.

1 — THE MORBIDITY OF PREGNANCY

When one considers the question of performing an abortion, one has accepted the fact of a pregnancy. Let us then consider the case of a woman who seeks an abortion for her own personal reasons: we may legitimately ask, disregarding the metaphysical questions concerning the rights of a fetus, whether it is medically safer that the pregnancy be allowed to continue naturally or be terminated as soon as possible. The pregnant woman can follow no course other than these two; and presumably it is this question which men of science are trying to answer by invoking morbidity statistics. Yet beyond comparing the overall *mortality* of abortion and of pregnancy in general, no attempt has been made to demonstrate the comparative *morbidity* of abortion and pregnancy. Data on the complications of therapeutic abortions are consistently published unaccompanied by control studies on the complications of allowing a pregnancy to continue. Thus one might note that in a series of Danish abortions performed by dilatation and evacuation, the incidence of significant hemorrhage was 4.6%.[3] However, the incidence of postpartum hemorrhage in term pregnancies is 5%[1], and in addition the incidence of third trimester antepartum hemorrhage is 3.5%.[1] Therefore, while terminating a pregnancy at ten weeks might expose a mother to a 4.6% chance of hemorrhage, failing to terminate her pregnancy would expose her to an even greater likelihood of hemorrhage at a later date. In addition, one might argue, she would have to spend several more months in a pregnant state, go through the pains of labour, deliver a child and perhaps raise one; and from any one particular mother's point of view all this might add considerably to the morbidity of her condition. Further, if one looks at the other complications of pregnancy it is disconcerting that people are allowed to become pregnant at all:

| | |
|---|---|
| antepartum hemorrhage | 3.8% |
| toxemia | 6 - 7 % |
| pyelonephritis | 2 % |
| hyperemesis gravidarum | 0.3% |
| cystitis | 3 % |
| dystocia, due to | |
| hypotonic inertia | 4 % |
| hypertonic inertia | 1 % |
| contracted pelvis | 5 % |
| postpartum hemorrhage | 5 % |
| puerperal infection | 1.4% |
| puerperal thromboembolism | 0.4% |

The above list[1] is exemplary, but demonstrates the flaw in the statement that by performing a therapeutic abortion one exposes the mother to a high risk of complications. One can just as easily claim to be saving her from a high risk of complications, and to a woman that does not want to be pregnant in the first place that might be a much happier outlook.

Another interesting set of statistics, to which both the Council of the Royal College and Eastman make reference, is that of Koya[7] in Japan. He listed several post-abortion morbidity statistics, including:

1) 22.9% had bleeding for more than four days within two weeks of operation;
2) 10.0% had fever lasting beyond two weeks;
3) 16.2% had abdominal pain for more than two weeks after operation; and a similar number had back pain.

He demonstrated that these results were significant by utilizing a carefully selected control population of non-pregnant women of similar age distribution who had never had induced abortions. However, he made no comparison with the incidence of such symptoms following

labour and delivery, having no control population of post-partum women. Until this other side of the question has been investigated, one cannot ever be sure that his statistics have not simply shown half the truth that the cause of the morbidity is not abortion at all, but pregnancy — in other words, that for a pregnant woman there is no easy way out.

## 2 — THE POPULATION UPON WHOM ABORTION IS PERFORMED

The second weakness in current therapeutic abortion statistics is their failure to acknowledge the nature of the population upon whom abortions are performed. In Canada and the United States, this population is certainly not randomly selected from the field of pregnant women. The most usual indication for abortion is a psychiatric disorder (up to 61% in a New York City series[5] and 34.4% in a series conducted at the Toronto General Hospital[6]). In the two series just cited, organic disease of the mother was an indication for abortion in 25% and 50% respectively. It is quite obvious that with such a selected population the incidence of post-partum complications is bound to be high. The only fatality in the TGH series was the result of a cerebral hemorrhage in a woman with chronic renal disease and hypertension.

In abortions conducted in Sweden, Denmark, Japan and, more recently, Britain, where the need for medical indications is not as strict as in North America, one can expect that the population of women having abortions will give a better picture of the morbidity of the operation itself, without the confounding effects of coincident organic diseases. However, in these more liberal countries one can expect that the population of women having abortions is still weighted, for even when abortion becomes a totally elective procedure it will be performed on a higher than random proportion of women with organic diseases that render their pregnancies hazardous under any circumstances. One wonders therefore why it is that published statistics do not specify which particular patients suffered those 5 to 15% of complications and those 0.07% of fatalities. Certainly a pregnant woman with hypertension and chronic renal failure is a high risk whether she is therapeutically aborted or carries to term; if she is always to be included in the former group, one can expect the morbidity statistics there to be duly more awesome. Furthermore, the question of legalizing *elective* therapeutic abortions is of more concern to the healthy woman between 16 and 40 years of age, who simply does not want her pregnancy, than to the woman with severe rheumatic heart disease to whom abortion will be advised in any case. Why, then, should the healthy woman be governed by decisions based on morbidity statistics derived from a population of less healthy women?

The truth of the implied hypothesis — that morbidity and mortality statistics in therapeutic abortion will show significant variation depending on the indications for abortion and the health of the mother — can be evaluated only in the light of a large series of cases. However, an unpublished review of 74 cases of therapeutic abortions performed at Women's College Hospital in Toronto over the past five years[8] offers evidence that such a large series would be fruitful.

This review, the major statistics of which will not be included, showed that, of the 74 cases, 9 (or 12.2%) had complications (disregarding 3 cases with fever equal to or greater than 100.4°F on the first post-operative day only). The following table shows the distribution of these complications according to the indication for abortion:

| Indications for abortion | No. of cases | No. of complications | % complicated |
|---|---|---|---|
| psychiatric disorders | 53 | 6 | 11 |
| organic disease of mother | 15 | 3 | 20 |
| fetal indications (rubella) | 6 | 0 | 0 |

Certainly conclusions cannot be drawn from such sparse evidence, but the series at least implies the value of a larger study.

## CONCLUSION

The discussion above has been intended to deal critically with the manner in which statistics have been used to provide part of the basis of a medical and legal point of view on therapeutic abortion. It is important to stress, before concluding, that the morbidity statistics referred to have been in terms of organic complications observed on a gynecological service. The *psychiatric* morbidity of therapeutic abortion has not been discussed, although the high incidence of psychiatric sequelae of therapeutic abortion (from 9% to 59% in various series[2]) leads one to expect that it is here that one will find the future of meaningful discussion on the hazards of therapeutic abortion.

*A. J. Shoichet* 6T9

*ACKNOWLEDGEMENTS*

*Special thanks to M. Weinstock 6T9 for help in reviewing cases at Women's College Hospital.*

[Students interested in the status of therapeutic abortion throughout the world, including some more recent mortality statistics, are referred to a review in the January 1969 issue of Scientific American, published since the writing of this article.]

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| | Vitamin $B_6$..... 0.6 mg. |

**Dosage**: Infants and children under 6 years of age, 5 drops daily; children 6 years and older, 8 to 10 drops daily.

Bottles of 8, 15, 30 and 50 cc., each with calibrated dropper for waste-free dosage.

*Full information on request.*

QUALITY PHARMACEUTICALS
Charles E. Frosst & Co.
MONTREAL CANADA
*FOUNDED IN CANADA IN 1899*